Lumbar facet joint injections for the management of chronic low back pain

Submitted by Saowarat Snidvongs to the University of Exeter
as a thesis for the degree of
Doctor of Medicine
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I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

Signature: ……

Overview and organisation of thesis

The overarching aims of this thesis are to review the existing evidence for the use of lumbar facet joint injections (FJIs) for the management of chronic low back pain (LBP), and to assess the feasibility of carrying out a definitive study to evaluate the effectiveness of FJIs in chronic LBP management. This thesis is organised as follows:

Chapter 1 presents the scientific background and rationale behind the management of chronic LBP and the need for a feasibility study, with an overview of the prevalence and burden of LBP, current management strategies, and the clinical practice guidelines based on the existing evidence. Chapter 2 details the literature search to identify systematic reviews of randomised controlled trials of intra-articular lumbar FJIs for chronic LBP management; the methodological quality of the included systematic reviews is assessed. Chapters 3 and 4 present the methods and results of the FACET feasibility study respectively. Funded by the National Institute for Health Research Health Technology Assessment programme and led by the author, this study aimed to assess the feasibility of conducting a definitive study to evaluate the clinical- and cost-effectiveness of FJIs compared with a sham procedure in patients with non-specific LBP of more than three months' duration. Chapter 5 discusses the results of the literature review and feasibility study, reflecting on the findings with regards to interpretation, generalisability and overall evidence. Recommendations for further systematic reviews and future clinical research are presented. Chapter 6 draws together the conclusions on the thesis with implications for clinical practice and healthcare policy.

Abstract

Background

Low back pain is a leading cause of disability worldwide and has a significant economic burden. Targeted lumbar facet joint injections may be used to relieve this pain and aid rehabilitation, but high quality clinical evidence to support their use is lacking. The National Institute for Health and Care Excellence (NICE) does not recommend spinal injections for the management of chronic low back pain.

Critical appraisal of systematic reviews

A critical appraisal of systematic reviews of randomised controlled trials concluded that the existing evidence to support the use of facet joint injections in low back pain management is equivocal, with methodological variability detected across the studies and reviews.

FACET feasibility study

The FACET feasibility study was a blinded parallel two-arm pilot randomised controlled trial to assess the feasibility of carrying out a definitive study evaluating the effectiveness of lumbar facet joint injections compared with a sham procedure, in patients with non-specific low back pain of more than three months' duration. The study recruited from the pain and spinal orthopaedic clinics at Barts Health NHS Trust only, although a multicentre study was planned.

Adult patients referred to the specialist clinics with non-specific low back pain despite NICE-recommended best non-invasive care were randomised and blinded to receive either intra-articular lumbar facet joint injections with steroid or a sham procedure, following a positive response to diagnostic medial branch nerve blocks. Both groups were invited to attend a combined physical and psychological programme.

Measures of feasibility included the recruitment and retention rate, and adherence to the study protocol. Questionnaires were used to assess a range of pain- and disability-related issues. Of 628 participants screened for eligibility, nine were randomised to receive the study intervention and eight participants completed the study.

Failure to recruit sufficient participants led to early closure of the study by the funder, and no conclusions were drawn on the clinical effectiveness of lumbar facet joint injections for the management of non-specific low back pain in this sub-group of patients. Although the target recruitment rate was not achieved, a robust study protocol was developed and the intended interventions delivered safely, thus addressing many of the feasibility objectives.

Conclusions

Further high quality randomised controlled trials and systematic reviews are required to inform decision makers, with implications for both clinical practice and policy. Stronger collaborations with primary care may improve the recruitment of patients earlier in their pain trajectory, suitable for inclusion in a future trial.

Study registration

EudraCT 2014-003187-20 and Current Controlled Trials ISRCTN12191542.

Funding details

The FACET feasibility study was funded by the National Institute for Health Research Health Technology Assessment programme (reference number HTA 11/31/02).

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Author's declaration and acknowledgements

I confirm that all the research work presented in this thesis is my own. My role in the lead up to the trial are as follows:

I was a member of the original co-applicant team for the FACET feasibility study, and co-ordinated and submitted the NIHR HTA programme grant application. I applied for the necessary research regulatory approvals and attended the research ethics committee meeting. I drafted the detailed project description and wrote the study protocol following discussions at the trial management group meetings. I designed the case report form and participant information sheet.

During the trial itself, I led the FACET feasibility study as the Principal Investigator at Barts Health NHS Trust; I recruited and consented patients to the study and carried out all the interventional pain procedures including the diagnostic injections, and the active and sham procedures. I presented the recruitment progress at each trial management group meeting. I am the first author of the study's output, which includes the final report to the study's funders and the monograph published in the NIHR's Journals Library.

I am however grateful to the following people for their support with the following aspects of the thesis:

Professor Rod Taylor (Professor of Health Services Research at the Institute of Health Research, University of Exeter Medical School; Director of the Exeter Clinical Trials Unit; and NIHR Senior Investigator) is my primary supervisor and the FACET feasibility study statistician. Although he undertook the statistical analyses for the study as described in the statistical analysis plan, I attended relevant training courses and understood the statistical analysis plan and processes. I did not carry out the statistical analyses as I was by necessity unblinded to correctly perform the interventional pain procedures.

Dr Vivek Mehta (Consultant in Pain Medicine at Barts Health NHS Trust; Director of the Pain and Anaesthesia Research Centre) is my secondary supervisor and offered advice and guidance throughout the process.

The FACET feasibility study team: Professor Richard Langford, Dr Vivek Mehta, Professor Rod Taylor, Dr Simon Thomson, Dr Manohar Sharma, Ms Angela Farr, Professor Deborah Fitzsimmons, Ms Stephanie Poulton, and Ms Alia Ahmad.

Dr Fausto Morell-Ducós (Specialty Registrar in Anaesthesia and Pain Medicine) was the independent second reviewer for the critical appraisal of systematic reviews.

Ms Isatou N'jie (Clinical Support Librarian at Barts Health NHS Trust) provided assistance in developing search terms for the literature searches.

Finally, I would like to thank family for their encouragement and support, in particular my mother Pasherin Snidvongs for the lumbar facet joint anatomy illustration.

Publications and presentations related to this thesis

The FACET feasibility study protocol was presented as a poster at the International Association for the Study of Pain's 16th World Congress on Pain in Yokohama, Japan (September 2016). The preliminary results were presented as a poster at the British Pain Society's 50th Anniversary Annual Scientific Meeting in Birmingham, UK (May 2017). The full study was presented as a poster at the European Pain Federation's 10th Congress in Copenhagen, Denmark; the critical appraisal of systematic reviews was also presented as a poster at the same congress (September 2017). The study was accepted as a poster presentation at the Society for Back Pain Research in Northampton, UK (November 2017) and the abstract will be published in the *Orthopaedic Proceedings* of the Bone & Joint Journal. The critical appraisal of systematic reviews won a poster prize and was presented at the 10th Annual Meeting of the Faculty of Pain Medicine of the Royal College of Anaesthetists in London, UK (December 2017).

The FACET feasibility study report, 'Facet-joint injections for non-specific low back pain: a feasibility RCT', has been published in the National Institute for Health Research Journals Library (*Health Technology Assessment* volume 21, number 74, December 2017)© Queen's Printer and Controller of HMSO 2017. This work was produced by Snidvongs *et al*. under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

List of abbreviations

AHRQ	Agency for Healthcare Research and Quality
AMSTAR	Assessment of Multiple Systematic Reviews
BeST	Back Skills Training
BPI	Brief Pain Inventory
CCG	Clinical Commissioning Group
CI	Confidence interval
CG	Clinical guideline
CONSORT	Consolidated Standards for Reporting Trials
CRF	Case report form
CPP	Combined physical and psychological (programme)
CT	Computed tomography
CTIMP	Clinical Trial of an Investigational Medicinal Product
DALY	Disability-adjusted life year
DMC	Data monitoring committee
FACET	Feasibility of Assessing the Clinical- and cost-Effectiveness of Therapeutic lumbar facet joint injections study
FJI	Facet joint injection
EQ-5D	EuroQol-5 Dimensions
EQ-5L-5L	EuroQol-5 Dimensions, five levels
GBD	Global Burden of Disease
GDG	Guideline Development Group
GP	General practitioner
HADS	Hospital Anxiety and Depression Scale
HRA	Health Research Authority
HTA	Health Technology Assessment
IMP	Investigational medicinal product
JRMO	Joint Research Management Office
LBP	Low back pain
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
NG	NICE guideline

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRS	Numerical rating scale
PI	Principal Investigator
PCS	Pain Catastrophizing Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSEQ	Pain Self Efficacy Questionnaire
RCT	Randomised controlled trial
REC	Research ethics committee
SD	Standard deviation
SF-12	12-item Short Form Health Survey
SF-MPQ-2	Short-Form McGill Pain Questionnaire version 2
SmPC	Summary of product characteristics
SPS	Stanford Presenteeism Scale
TMG	Trial management group
TSC	Trial steering committee
VAS	Visual analogue scale
YLD	Years lived with disability

Chapter 1: Introduction

The prevalence and burden of low back pain

Low back pain (LBP) is a significant problem worldwide; an updated systematic review of its global prevalence has shown that the mean lifetime prevalence of activity-limiting LBP is 38.9%, with an annual prevalence of 38%.[1] This group defined severe chronic LBP as 'constant low back pain, which causes difficulty dressing, sitting, standing, walking and lifting things. The person sleeps poorly and feels worried'.[2] The Declaration of Montréal, agreed at the International Pain Summit in 2010, has stated that access to pain management is a fundamental human right.[3]

The Global Burden of Disease (GBD) project aims to integrate all existing healthcare knowledge into a universal framework to quantify levels and trends in health. The most recent GBD study published in 2016, examining worldwide observational epidemiological trends in disease, injuries and risk factors since 1990 estimated that the prevalence of LBP has increased by over 17% between 2005 and 2015, a possible reflection on improving health and longer life expectancy, but decreasing overall functional health. Occupational ergonomic factors were also suggested to play a significant role in the development of LBP. The global burden of chronic pain is expected to continue to increase, in parallel with the burden of disabling non-communicable disease conditions.[4]

LBP was the leading cause of years lived with disability (YLDs) in 2015, causing more disability globally than any other condition in most countries, and all high-income countries.[5] LBP remained the leading case of YLDs in 2016.[6] In 1990 low back and neck pain was the 12th leading cause of global disability-adjusted life years (DALYs), an expression of burden and quantified as a year of life lost for each DALY; this increased in 2005 and 2015 to 8th and 4th positions respectively.[7] In the United Kingdom, the same systematic analysis concluded that low back and neck pain represented the second leading cause of DALYs in 2015, behind ischaemic heart disease.

LBP has an economic burden not only on health service providers, but also on the individual. Estimates of healthcare costs can vary even within the same country, with cost discrepancies being described at a local level in one review paper.[8] The direct costs (such as for hospital services and medications) associated with back pain in the United Kingdom in 1998 was estimated to be £1632 million, which was approximately 20% of total health expenditure that year. Approximately 35% was incurred within the private sector, in contrast to employment and informal care costs, which ranged from a conservative estimate of £5018 million to an upper estimate of £10 668 million.[9] As the most recent direct financial cost estimates for the United Kingdom were published twenty years ago, it is likely that the current costs may be significantly greater due to inflation and other changes to the economic and political landscape. The indirect costs may be substantially greater still. The inconsistencies of pain service provision across the United Kingdom is detailed in the final report of the National Pain Audit published in 2012.[10]

One systematic review identified a number of studies that have attempted to estimate the direct, indirect and total costs of LBP in the United States and internationally.[11] The review concluded that LBP represented an important economic burden worldwide, but methodological differences meant that it was difficult to compare the costs across studies and between countries. It again noted however that outside the United States, the direct costs were relatively low compared with indirect costs, which relate to productivity and employment. Although estimation of societal costs was outside the scope of this review, it inferred that interventions that have the potential to reduce LBP and associated disability claims may present an opportunity to reduce the economic burden in the long term.

General overview of chronic low back pain management

LBP can be defined as pain, muscle tension, or stiffness localised below the costal margin and above the inferior gluteal folds, with or without leg pain.[12]

Non-specific LBP, where symptoms are experienced without any recognisable pathology,[13] is thought to affect around 90% of all LBP sufferers; between 1 to 5% of patients presenting with LBP will have a serious spinal pathology, such as vertebral fractures, malignancy, infection, and inflammatory disease.[14]

A number of individual risk factors have been identified from twenty prospective studies which may predict the development of persistent disabling LBP; these include maladaptive pain coping behaviours such as fear avoidance behaviour, nonorganic signs (including an exaggerated painful response, or non-reproducible pain), functional impairment, general health status, and psychiatric co-morbidities.[15] Although it is believed that the majority of those affected with LBP will recover within a few months, others will develop chronic symptoms and experience recurrent episodes.[16] Other early prognostic indicators contributing to the transition from acute to chronic LBP with disability at 12 months after onset include being unemployed, having widespread pain, a high level of pain disability as assessed using the Chronic Pain Grade, catastrophising, and fear of pain.[17] Screening tools may be used in the primary care setting to identify risk factors for a poor disability outcome and prolonged absenteeism from work, which have the potential to affect future care decisions.[18]

In 2015, the International Association for the Study of Pain (IASP) established a task force to propose a new category for chronic pain in the 11th revision of the International Classification of Diseases (ICD) of the World Health Organisation, stating that chronic pain is not represented adequately in the current 10th revision ICD-10. In the proposal, chronic pain is defined as 'persistent or recurrent pain lasting longer than three months' and chronic primary pain is 'pain in one or more anatomic regions that persists and recurs for longer than three months and is associated with significant emotional distress or significant functional disability (interference with activities of daily living and participation in social roles) and that cannot be explained by another chronic pain condition'.[19] Non-specific chronic LBP will be categorised as 'localised chronic primary pain'.

There remains a lack of gold standard for the diagnosis of chronic LBP. One systematic review of diagnostic tests to identify the tissue source of LBP from potentially pain-generating sites such as the intervertebral disc, facet joint or

sacroiliac joint concluded that diagnostic tests were of questionable value in clinical practice especially in formulating treatment options.[20] Diagnostic imaging for LBP, such as the routine use of computed tomography (CT) or magnetic resonance imaging (MRI), has not been shown to improve clinical outcomes in a meta-analysis of six randomised controlled trials funded by the American Pain Society,[21] and are not recommended in many clinical practice guidelines unless features of serious spinal pathology ('red flags') are suspected.

A number of treatment options are available for the management of chronic LBP. These range from conservative treatments (including acupuncture, medications, pain management programmes and physical therapies) to spinal injections and surgery. Some of these management strategies will be discussed in further detail in this chapter.

Non-specific LBP research is considered challenging due to the lack of gold standards in inclusion criteria, definitions, assessments and outcome measures; this heterogeneity has meant that it was not always possible to compare studies.[22] In 2014, a Research Task Force of the National Institutes of Health Pain Consortium developed research standards for chronic low back studies,[23] potentially allowing for pain phenotyping, and facilitating comparisons between studies.

Clinical practice guidelines

Clinical practice guidelines for the management of LBP exist in more than 13 countries, including the United Kingdom, France, Germany, Canada, and the United States.[24] National healthcare decisions are often informed and influenced by specific programmes or independent agencies including The National Institute for Health and Care Excellence (NICE) in the United Kingdom, the Haute Autorité de Santé (HAS) in France, the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany, the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Effective Health Care Program

(EPC) of the Agency for Healthcare Research and Quality (AHRQ) in the United States. These groups aim to increase the value of healthcare services and improve national decision making despite increasing healthcare expenditures and limited resources, utilising systematic reviews of technologies or healthcare interventions in guideline development. The use of graded recommendations based on the best available quality evidence may therefore reduce variations in the quality of care both nationally and worldwide.

These international guidelines generally have consensus on many recommendations for chronic LBP management. Table 1 summarises some of these recommendations.

Table 1. International clinical guidelines and recommendations on the treatment of low back pain. Adapted from Table 49-3, Melzack and Wall's Textbook of Pain 6th edition (2013).[12] The United Kingdom guidelines were written after the textbook was published and are adapted from NICE guideline NG59 'Low back pain and sciatica in over 16s: assessment and management' (2016)[25]

Country	Education	Medication	Exercises	Manipulation	Bed rest	Referral to specialist
United Kingdom (2016)[25]	Provide people with advice and information, tailored to their needs and capabilities, to help them self-manage their LBP with or without sciatica, at all steps of the treatment pathway	Oral NSAIDs at the lowest effective dose for the shortest possible period of time Consider weak opioids (with or without paracetamol) for managing acute LBP only if an NSAID is contraindicated, not tolerated or	Consider a group exercise programme (biomechanical, aerobic, mind–body or a combination of approaches) within the NHS for people with a specific episode or flare-up of LBP with or without sciatica Take people's specific needs,	Do not offer traction for managing LBP with or without sciatica Consider manual therapy (spinal manipulation, mobilisation or soft tissue techniques such as massage) for managing LBP with or without sciatica, but only	No recommendation	Consider referral for assessment for radiofrequency denervation for people with chronic LBP when non-surgical treatment has not worked for them and the main source of pain is thought to come from structures supplied by the medial branch nerve and they have moderate or severe levels of localised back pain (rated as 5 or more on a visual analogue scale, or

Country	Education	Medication	Exercises	Manipulation	Bed rest	Referral to specialist
	Include information on the nature of LBP and sciatica and encouragement to continue with normal activities	has been ineffective Do not offer paracetamol, opioids, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants or anticonvulsants	preferences and capabilities into account when choosing the type of exercise	as part of a treatment package including exercise, with or without psychological therapy		equivalent) at the time of referral Only perform radiofrequency denervation in people with chronic LBP after a positive response to a diagnostic medial branch block Consider spinal decompression for people with sciatica when non-surgical treatment has not improved pain or function and their radiological findings are consistent with sciatic symptoms
France (2000)	Short-term education about the back, in groups, is not beneficial	Acute and chronic: regular simple analgesics, NSAIDs, and	Acute: flexion exercises have not been shown to be of benefit. No	Acute and chronic: provides short-term benefit. No recommendation	Acute and chronic: not recommended	Acute: no recommendation Chronic: recommended physiotherapy/behavioural

Country	Education	Medication	Exercises	Manipulation	Bed rest	Referral to specialist
		muscle relaxants. No evidence for systemic corticosteroids Chronic: additional recommendations for acetylsalicylic acid, level II following failure to respond to level I and level III (strong opioids) on case-by-case basis. Tetrazepam, tricyclic antidepressants	recommendation on extension exercises Chronic: physical exercise is recommended; no particular type advocated	for one form of manual therapy over another		therapy/multidisciplinary program if non-response to first-line care
Germany (2007)	Acute: stimulate daily activities, explain that	Acute and chronic: (1) paracetamol, (2) NSAIDs (oral or	Acute: exercise therapy not effective	Acute: optional within the first 4–6 weeks	Maximum of 2 days' bed rest	Immediate surgery indicated for cauda equina syndrome

Country	Education	Medication	Exercises	Manipulation	Bed rest	Referral to specialist
	moving is not dangerous Chronic: more intense psychotherapy indicated in case of psychological co-morbidity	topical), (3) muscle relaxants (in patients with muscle spasms, (4) opioids	Subacute and chronic: exercise therapy well supported by evidence	Chronic: option if short lasting		Optional referral for surgery: therapy-resistant (>6 weeks) plus signs of nerve root compression Surgery may be an option if after 2 years' conservative treatment, including a biopsychosocial treatment program, was unsuccessful
Canada (2007)	Reassurance and advice to return to work and usual activities	NSAIDs, muscle relaxants, and analgesics for acute pain Low evidence for NSAIDs and analgesics for subacute pain	Strengthening exercises, extension exercises, and specific exercises not recommended for acute but recommended for subacute and chronic pain with	Acute: recommended for short-term pain reduction Subacute and chronic: recommended with low evidence	Not recommended	Refer patients with neurological signs or symptoms if functional deficits persistent or deteriorating after 4 weeks

Country	Education	Medication	Exercises	Manipulation	Bed rest	Referral to specialist
			no superior form of exercise			
United States (2007)	Provide information on prognosis, staying active, self-management Self-care education books recommended	Paracetamol, NSAIDs recommended as first-line drugs Acute: muscle relaxants, benzodiazepines, tramadol, opioids Subacute or chronic: antidepressants, benzodiazepines, tramadol, opioids	Acute: not effective Subacute and chronic: recommended	For acute LBP if not improving	Even if required for severe symptoms, patients should be encouraged to return to normal activities as soon as possible	For interdisciplinary intervention if chronic If suspicion of significant nerve root impingement or spinal stenosis

Controversies arising from the clinical practice guidelines

Guidelines in the United Kingdom

In May 2009, NICE published clinical guideline 88 (CG88), 'Low back pain: early management of persistent non-specific low back pain'. Its aim, based on the 'best available evidence', was to advise healthcare professionals such as general practitioners (GPs) on the management of tension, soreness and stiffness in the low back (between the rib cage and buttock creases) without a specific cause, which lasted for more than six weeks but less than twelve months.[26]

NICE CG88's Guideline Development Group (GDG) aimed to answer the research question, 'What is the effectiveness of injections or nerve blocks compared with usual care or sham on pain, functional disability or psychological distress?'.[26] One systematic review of lumbar facet joint injections in chronic LBP management was identified,[27] and one randomised controlled trial met the inclusion criteria; this was double-blind, placebo-controlled randomised controlled trial published by Carette *et al.* which compared intra-articular lumbar facet joint injections with steroid against intra-articular saline injections, in participants who had a positive response to a single diagnostic block.[28]

NICE CG88's GDG did not recommend injections of therapeutic substances into the back for non-specific LBP due to insufficient evidence, advising instead a more conservative approach including exercise, spinal manipulation and acupuncture (see figure 1). The Faculty of Pain Medicine of the Royal College of Anaesthetists had expressed concerns over these guidelines, as their nominated pain medicine specialist and expert in non-surgical inventions was not selected for membership of the GDG.[29] They issued stakeholder comments to the draft guideline in November 2008, which concluded:

'National guidelines for this common clinical problem would be very helpful but these current recommendations are seriously flawed and not suitable for a

NICE publication. We believe that there are insurmountable problems with the methodology used by the Guideline Development Group, the strength of available evidence, the interpretation of the data and therefore conclusions and recommendations. Significantly more work needs to be undertaken on this topic with input from others who will be able to assist in the appropriate interpretation of the available (but scant) evidence.'[30]

The publication of these guidelines led to the resignation of the President of the British Pain Society,[31] and concerns were expressed that funding for pain clinics and services may be reduced as a direct consequence.[32] The Council of the British Pain Society recommended withdrawal of the guidelines in a consensus statement published in their Autumn 2009 newsletter.[33]

In November 2016, NICE CG88 was replaced by NICE guideline 59 (NG59), 'Low back pain and sciatica in over 16s: assessment and management'.[25] The updated guideline had an expanded remit and advised consideration of radiofrequency denervation in the management of LBP after a positive response to a diagnostic medial branch block, in cases where non-surgical treatment had failed.

NICE NG59's GDG explored the research question, 'What is the clinical and cost effectiveness of spinal injections in the management of non-specific low back pain?'.[25] The interventions and comparators in the review protocol included steroid, local anaesthetic, sclerosants, Botox and hyaluronans, and were to be compared versus each other and also with a sham, placebo or saline, usual care, or other treatments. Six image-guided intra-articular lumbar facet joint injection studies were identified and split into pre-defined sub-groups. Studies of monotherapy[28, 34, 35] and combination therapy[36-38] were reviewed by the GDG.

The two GDGs differed in terms of the composition of the group members (for example, an interventional pain specialist was represented in NICE NG59's group), and in how the included studies were identified; NICE CG88's GDG identified a randomised controlled trial from a systematic review paper, whereas NG59's GDG published a new clinical review protocol.[39]

Different interpretations can be applied to the same study; one example is the study published by Carette *et al.* in 1991, which NICE CG88's GDG concluded, in concordance with the study's authors themselves, showed little value in intra-articular steroid injections for chronic LBP management.[28] NG59's GDG noted that although there was a change in the Mean Sickness Impact Profile in favour of the steroid group at six months, it was not clear what a meaningful magnitude of change was. Staal and colleagues however concluded that this study had 'positive results' in their Cochrane review.[40] This indicates that study outcomes can be difficult to interpret clinically; statistically significant results may not have clinical relevance for example, and are therefore open to interpretation.

Some of the differences between the included studies can be attributed to the dates of the literature searches; December 2006 and December 2015 for NICE CG88 and NICE NG59 respectively. The single study used for guideline development by NICE CG88's GDG compared facet joint injections with a sham procedure, whereas NICE NG59's GDG included comparator trials in addition to a placebo study, and studies with a usual care arm. Although NICE NG59's GDG noted that there was heterogeneity between the trials, spinal injections were again not recommended for managing LBP based on their summary of the evidence (see figure 2). Despite their differences in some aspects of their deliberation, both GDGs drew the same final conclusions with regards to lumbar facet joint injections.

LBP and sciatica were selected by the Trauma Programme of Care Board as their Pathfinder Project; these projects were established by NHS England in 2013 in order to set up clear 'end-to-end' generic pathways from primary care into specialised services as required, enabling collaborative commissioning and incorporation of the latest evidence into the pathways.[41] The National Low Back and Radicular Pain Pathway 2017 was updated following the publication of the NICE guidelines NG59, and included all of NICE's recommendations (see figure 3).

Figure 1. Flowchart for the management of persistent non-specific low back pain (NICE CG88, 2009). Adapted from 'Low back pain: early management of persistent non-specific low back pain' (NICE clinical guideline 88). Quick reference guide[42]

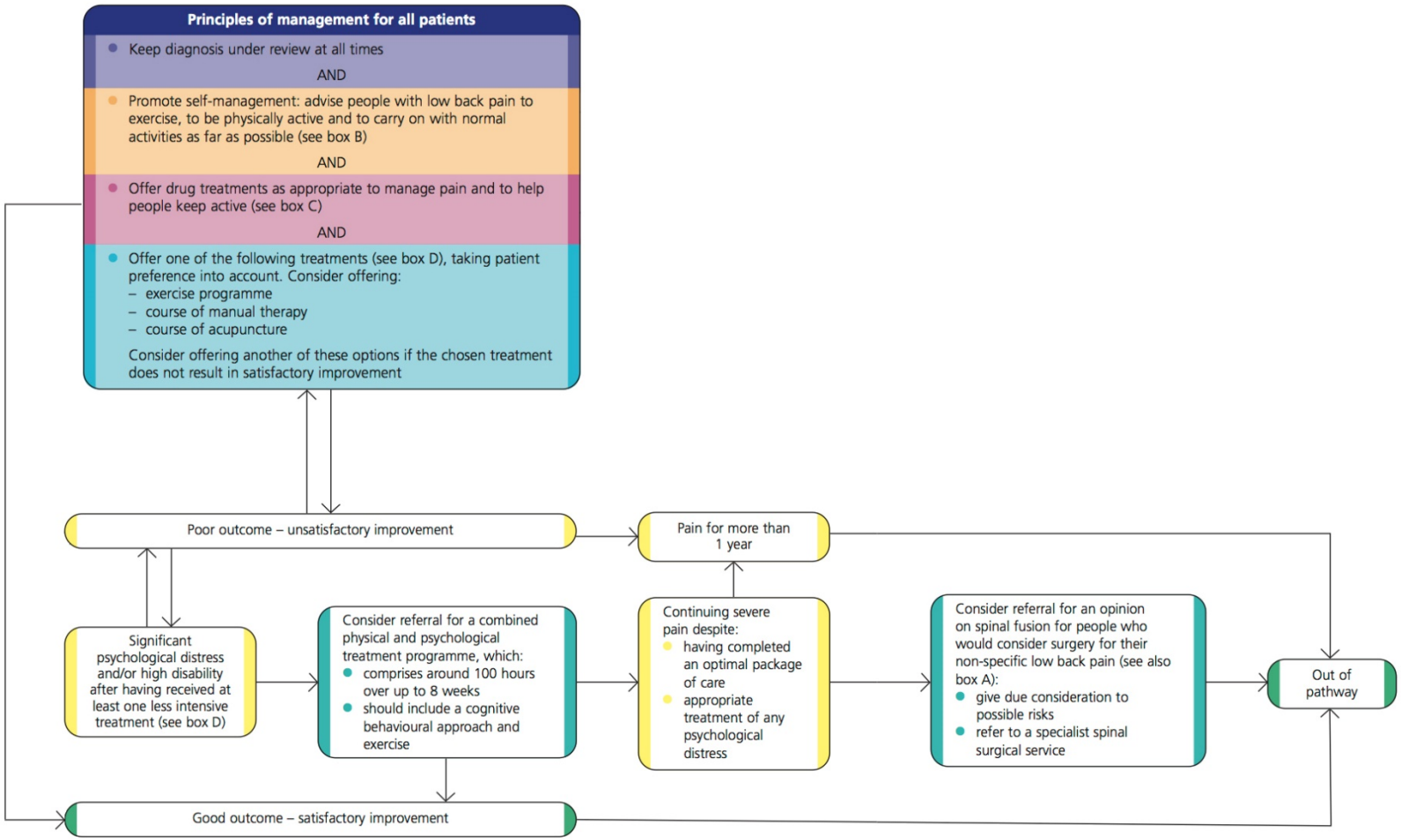


Figure 2. NICE Pathways. Managing low back pain and sciatica (NICE NG59, 2016). Adapted from the interactive NICE Pathways http://pathways.nice.org.uk/pathways/low-back-pain-and-sciatica[43]

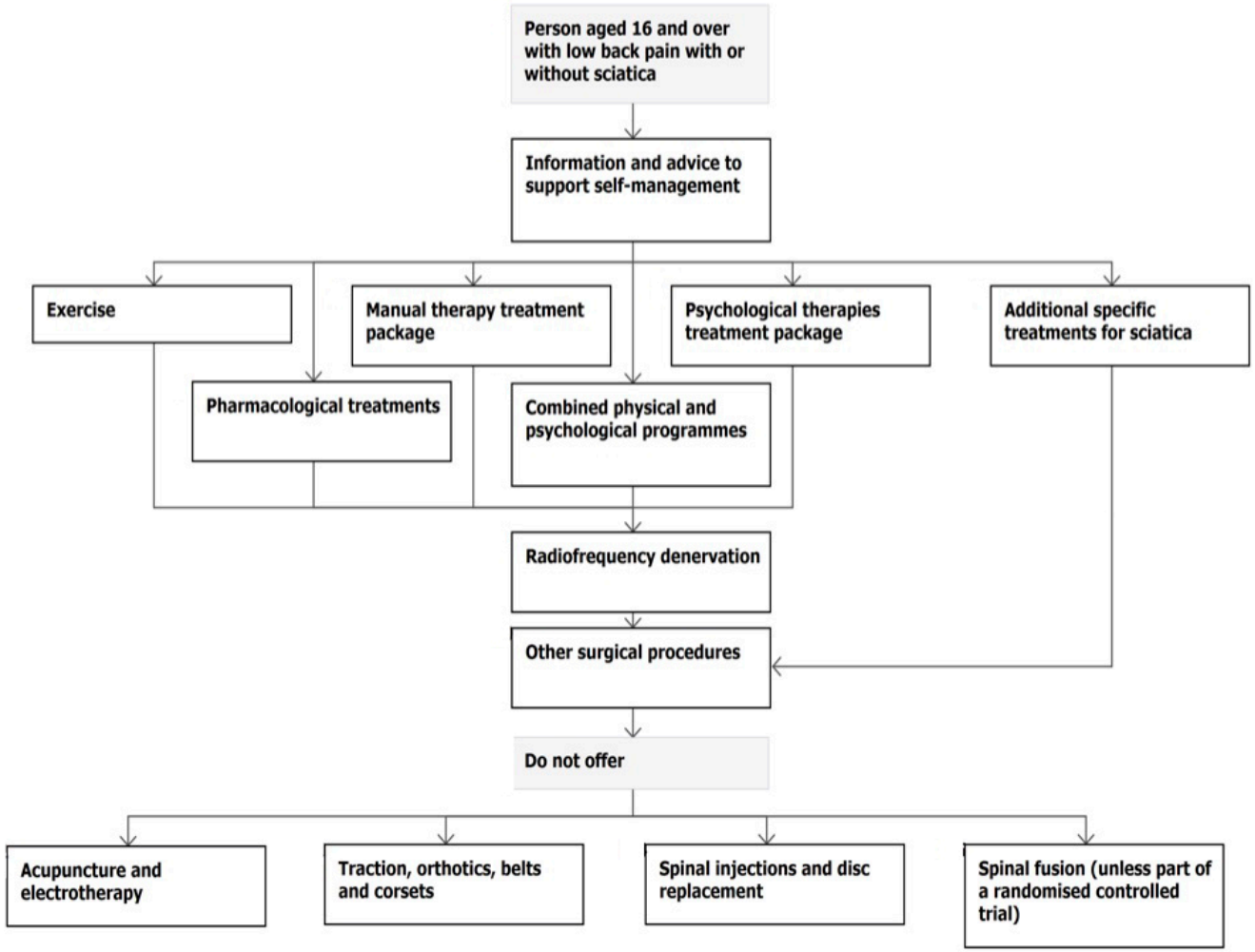
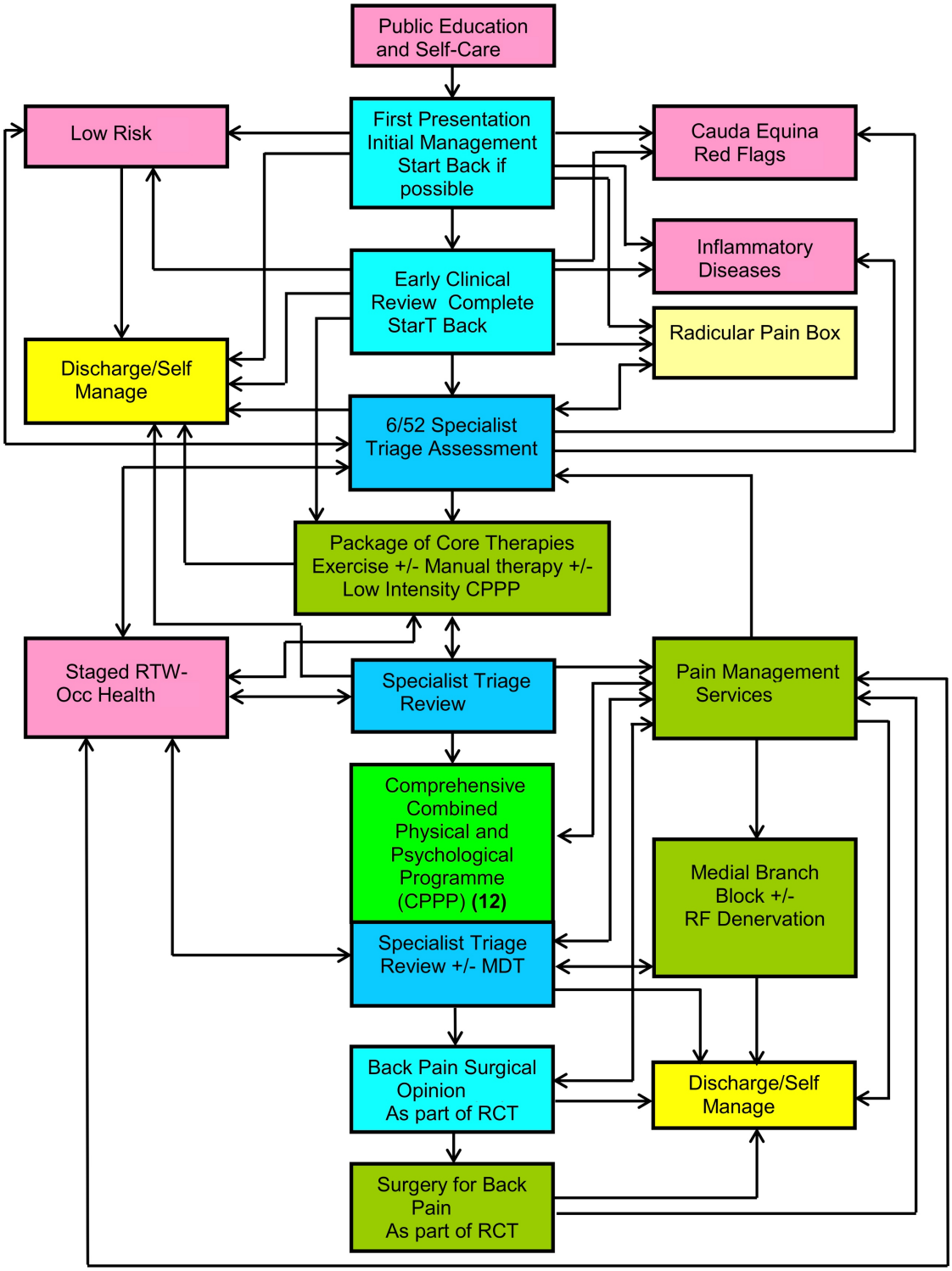


Figure 3. Back pain pathway flowchart from the National Back Pain and Radicular Pain Pathway. Adapted from NHS England's Trauma Programme of Care, National Radicular Pain Pathway 2017[41]



Guidelines in the United States

In concordance with the NICE guidelines in the United Kingdom, the American Pain Society similarly do not recommend facet joint injections with steroid for persistent non-radicular LBP, based on 'moderate-quality evidence';[44] the authors however stated that future research could change these recommendations. These guidelines were criticised by Manchikanti and colleagues in 2010, who described a number of alleged methodological failures and inappropriate analyses, potentially resulting in misleading conclusions.[45]

The views expressed by the American Pain Society have also been challenged by the American Society of Interventional Pain Physicians in their 2013 publication 'An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. Part II: guidance and recommendations'.[46] This group reviewed a number of spinal interventional procedures and found limited evidence to support the use of intra-articular lumbar facet joint injections based on the results of one moderate quality randomised controlled trial and five observational studies.

Potential implications of the clinical practice guidelines

Despite the widespread availability of clinical guidelines for the management of non-specific LBP in various countries, adherence to these guidelines have been demonstrated to be suboptimal; one systematic review and meta-synthesis of qualitative studies has identified a number of implementation barriers in guideline adherence by primary care providers including GPs and physiotherapists.[47] The authors concluded that clinicians had an inherent lack of trust in the guideline development process and in their dissemination, and that the guidelines were perceived to be lacking in credibility. One finding from this review was that clinicians tended to adopt a biomedical approach to LBP management (seeing pain as a symptom of a physical disorder), rather than utilising a biopsychosocial model, where the physical, psychological and social components of pain are considered together. Popular clinical practice included

the use of imaging techniques and interventions against current guideline recommendations.

A review of utilisation of interventional pain techniques in the fee-for-service Medicare population, the largest insurer in the United States, showed that there was an annual increase of 10.7% (overall increase of 313%) in facet joint interventions and sacroiliac joint blocks between 2000 and 2014.[48] Beckworth and colleagues noted that between 2007 and 2012 approximately 1.5 million lumbosacral facet joint injections were being carried in the Medicare population each year, with an average increase of 11% per year from 2000 until 2012.[49] These figures have however been challenged by Manchikanti and colleagues, citing methodological issues and the inclusion of denied services.[50] Both groups however acknowledge a decline in growth per year from 2010, when billing became limited to image-guided injections only (fluoroscopic or CT-guided), of no more than three spinal levels.

In the United Kingdom, Hospital Episode Statistics record the number of procedures carried out using the procedural classification Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4 (OPCS-4).[51] A search for the code V54.4 'Injection of spinal facet of spine', carried out on 1st December 2017, gave an estimate of the number of facet joint injections carried out per year in England (see figure 4). These figures demonstrate a generally increasing trend in the numbers of procedures carried out each year, although the accuracy of these figures is unclear. The plateau in growth in recent years may reflect policy changes as a result of the NICE guidelines published in 2009 and 2016.[25, 26]

Comparison of the percent changes of recorded facet joint injections and interventional pain procedures each year between the United States and England show comparable trends in the rate of growth and decline of these procedures being carried out (see table 2). This may again reflect policy changes at a government level such as the introduction of the Affordable Care Act in the United States, and changes in how the fee-for-service codes were being applied (see figure 5).

Table 2. Percent change in facet joint injections and interventional pain procedures recorded in England and the United States compared to the previous year

Year	Percent change in facet joint injections and interventional pain procedures recorded compared to the previous year (%)		
	England (data from Hospital Episode Statistics)[51]	United States (Manchikanti *et al.*)[48]	United States (Beckworth *et al.*)[49]
2001	+14.3	+18.6	+25
2002	+10.7	+22.6	+26
2003	+5.1	+15.5	+25
2004	+9.2	+28.4	+23
2005	+20.9	+7.8	+23
2006	+13.2	+11.1	+25
2007	+25.4	-2.9	-5
2008	+19.2	+5.1	+1
2009	+9.7	+3.9	0
2010	+6.2	-3.8	-14
2011	-7.8	+2.2	+3
2012	+12.2	-1.3	0
2013	+7.4	-3.4	n/a
2014	+9.1	-1.2	n/a

Figure 4. Number of OPCS-4 V54.4 'Injection of spinal facet of spine' procedures recorded per year in England.

Search carried out on 1st December 2017.

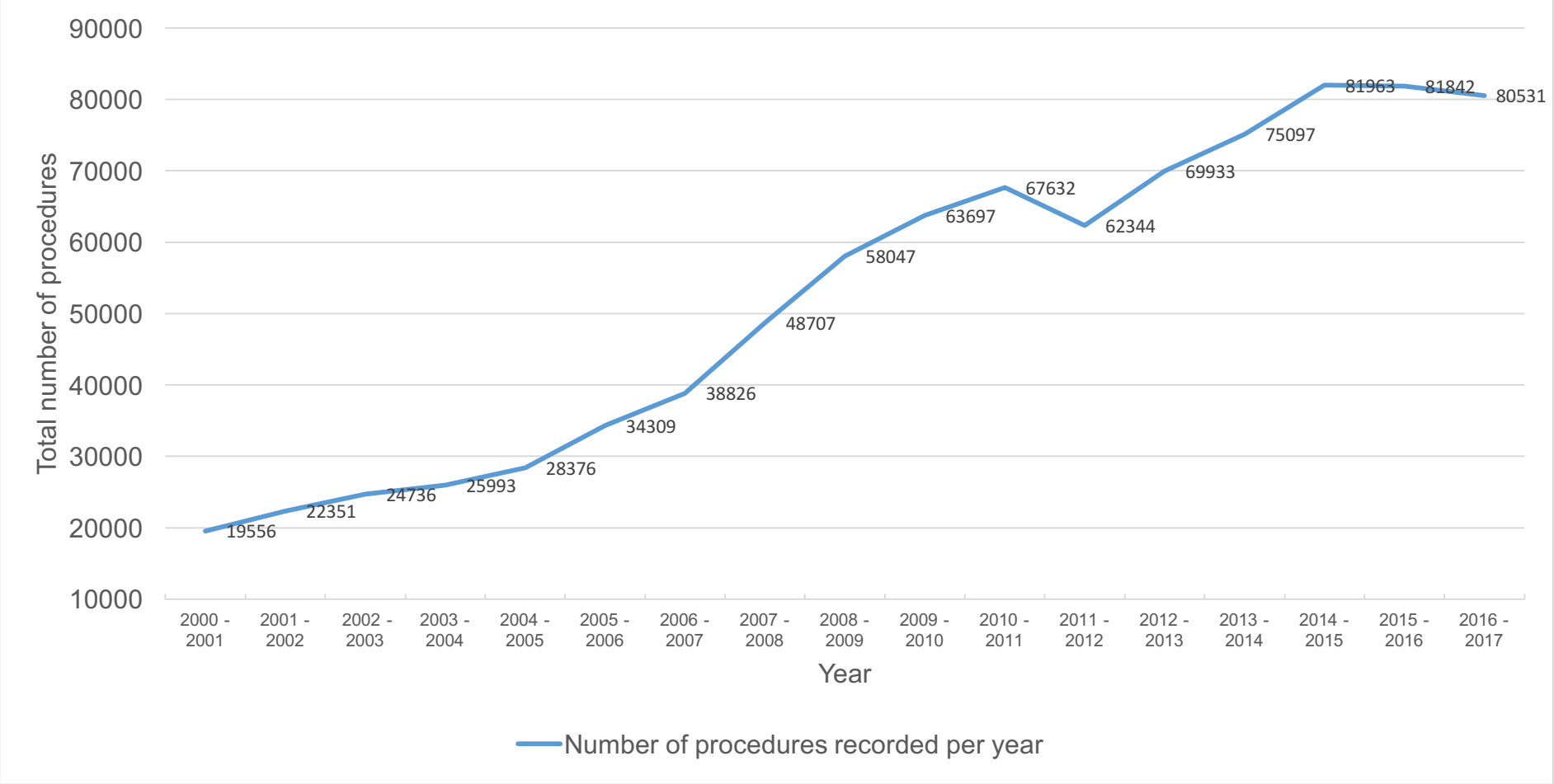
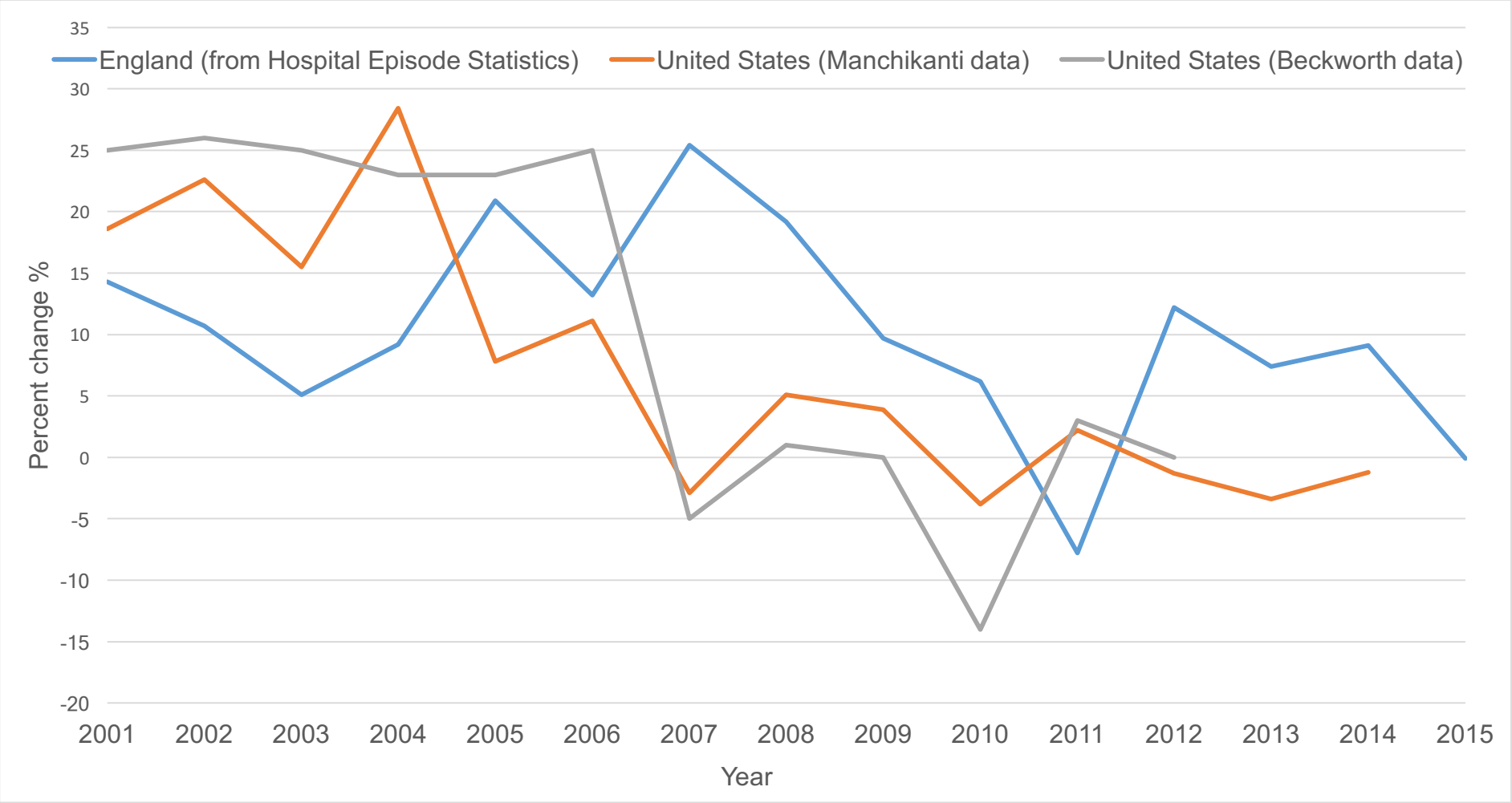


Figure 5. Percent change in facet joint injections and interventional pain procedures recorded in England and the United States compared to the previous year, between 2001 and 2015



Diagnosis of low back pain of facet joint origin

A number of anatomical structures within the low back are associated with the development and persistence of LBP, including the facet joints, sacroiliac joints, intervertebral discs, ligaments, soft tissue and fascia, muscle, and nerve roots. Lumbar facet joints, also known as zygapophyseal joints, are paired synovial joints between the superior and inferior articular processes of consecutive lumbar vertebrae, and between the fifth lumbar vertebra and the sacrum (see figure 6). Their role is to provide structure and integrity to the lumbar spine, and to guide movement, including flexion-extension and some rotation. These facet joints are innervated by free and encapsulated nerve endings supplied by the medial branches of the dorsal rami ('medial branch nerves'), which neuroanatomic studies have shown to contain substance P and calcitonin gene-related peptide.[52] Pain perceived from the facet joint can be considered to arise from any structure that is part of the joint, including the fibrous capsule, synovial membrane, hyaline cartilage, and bone. One evidence-based review has estimated the prevalence of lumbar facet joint pain to be between 5 and 15% of the axial LBP population, although the prevalence increases with age.[53]

The diagnosis of facet joint pain at present is largely a clinical one, based on history and physical examination. Typically, sufferers complain of bilateral axial LBP which may be referred to the groin or thigh, rarely distal to the knee. Lumbar paraspinal tenderness has been shown to be associated with a successful outcome following lumbar facet joint interventions, and is considered a reliable indicator of pain of facet joint origin.[54] Revel and colleagues described a number of clinical characteristics for lumbar facet joint pain in their 1998 publication 'Capacity of the clinical picture to characterize low back pain relieved by facet join anesthesia';[55] these include:

- Pain not worsened when rising from forward flexion
- Pain well relieved by recumbency
- Pain not exacerbated by coughing
- Pain not worsened by extension-rotation
- Pain not worsened by hyperextension

These tests have however not been shown to be a useful clinical screening tool for lumbar facet joint interventions, with one study demonstrating the test's low sensitivity and high specificity.[56] One modified Delphi survey of pain experts reached a consensus on indicators of LBP of facet joint origin, which included pain on palpation of the facet joint or transverse process, worsening pain on trunk extension but not flexion, paravertebral muscle spasm over the affected joint, no pain referral below the knee, and no radicular symptoms.[57]

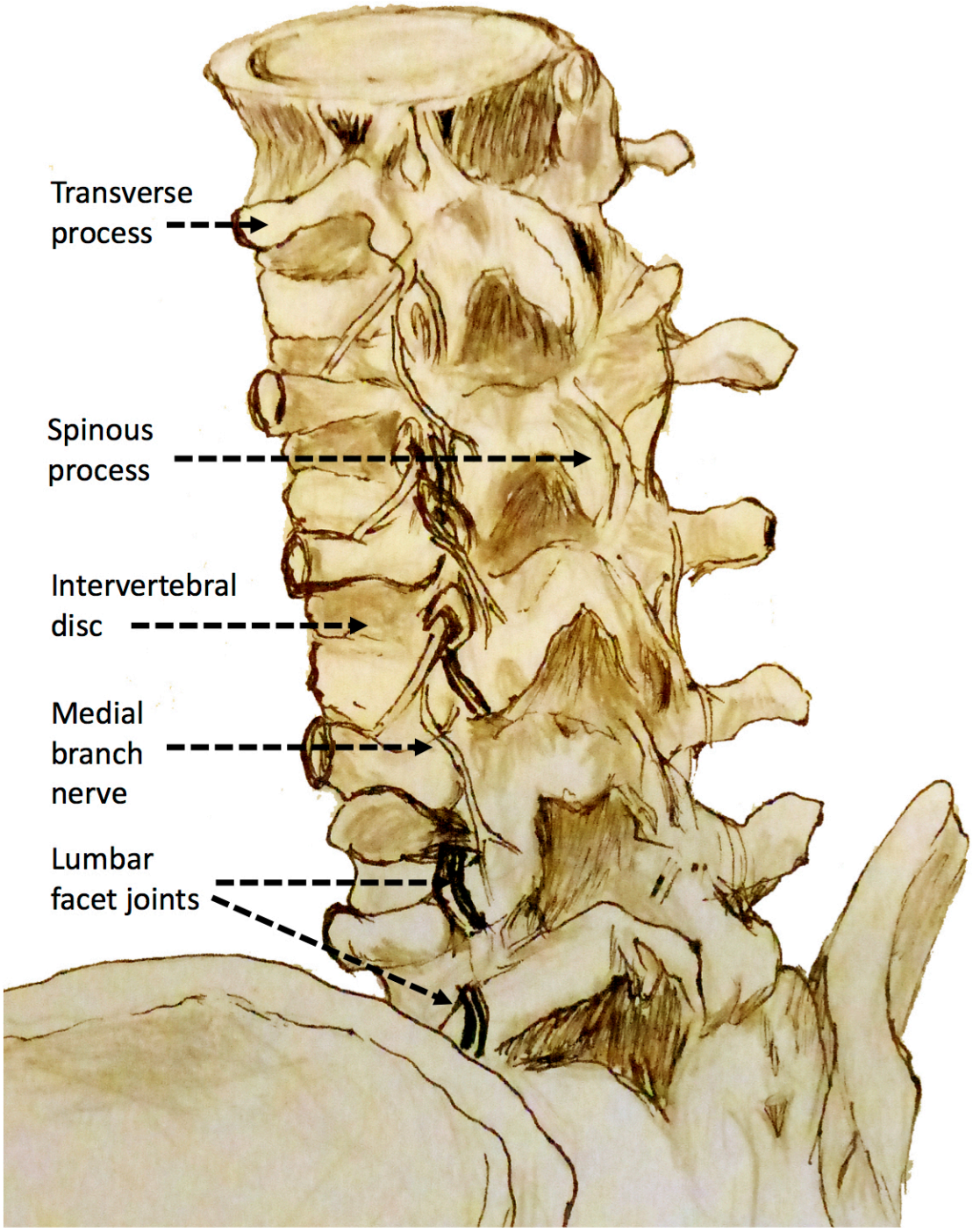
As discussed in the previous section, the existing clinical guidelines do not recommend routine imaging in the management of LBP unless there are features of serious spinal pathology. Computed tomography (CT) imaging is considered to be a preferred method for demonstrating evidence of facet joint arthritis although Kalichman and colleagues have concluded that the association between facet joint osteoarthritis as seen on CT imaging and LBP remains unclear.[58] This group carried out a cross-sectional study of a community-based population with 188 participants and found a prevalence of facet joint arthritis (as diagnosed on CT imaging) of 59.6% in men and 66.7% in women which increased with age, with the highest prevalence at the L4/5 spinal level. No significant association between facet joint arthritis and LBP was found.

Diagnostic injections may be utilised to help diagnose LBP of facet joint origin, usually prior to further spinal interventions. These involve an injection of local anaesthetic either into the joint itself, or more commonly to its nerve supply, the medial branch nerves. A positive response to a diagnostic block is a reduction in pain for the duration of the local anaesthetic's action, although single blocks may be associated with a false positive response.[59] Dual or double comparative blocks can be used, where the procedure is repeated with a different local anaesthetic, which has a different duration of action. Lidocaine (a short-acting local anaesthetic) and bupivacaine (a longer-acting local anaesthetic) are commonly used. Placebo-controlled blocks and triple comparative blocks have also been used and are described in the literature.

A multicentre, randomised controlled trial of 151 participants in the United States has concluded that it is more cost-effective to proceed immediately to radiofrequency denervation of the lumbar facet joint medial branch nerves, without first carrying out diagnostic blocks. The group receiving no diagnostic blocks had the highest number of total successful procedures after three months, compared with the groups who received single or dual blocks.[60]

In recent years, a number of systematic reviews have been published on the diagnostic accuracy and utility of lumbar facet medial branch nerve blocks, often reviewing randomised controlled trials from the same groups of authors.[61-63] Falco and colleagues published an updated review in 2012, concluding that there is good evidence for the use of dual blocks with 75% to 100% pain relief as the criterion standard.[61] Boswell and colleagues demonstrated level 1 evidence for the use of dual blocks in diagnosing chronic lumbar facet joint pain, based on evidence obtained from multiple relevant high quality randomised controlled trials and diagnostic accuracy studies.[62] Manchikanti and colleagues reviewed 7 controlled diagnostic studies with 80% or more pain relief, and 6 studies with at least 75% pain relief, and again concluded that there was level 1 evidence to support their use.[63]

Figure 6. Lumbar facet joint anatomy



Therapeutic lumbar facet joint interventions

LBP of facet joint origin can be treated with spinal injections including lumbar facet joint injections, medial branch nerve blocks, and radiofrequency denervation of the medial branch nerves. At present, there is no consensus or gold standard on their indications or the technique of these procedures. These injections can be used to serve both a therapeutic and a diagnostic purpose; this appears to be common practice in the United Kingdom, to presumably avoid the need to return for further interventions.[64]

Lumbar facet joint injections involve the injection of an active substance, such as steroids with or without a local anaesthetic, into the joint itself (intra-articular injections), or next to the joint (peri-articular injections). They are commonly carried out under x-ray or fluoroscopic guidance, although can be performed under ultrasound or CT guidance.[65] The NICE Guideline Development Group for the guideline NG59 'Low back pain and sciatica in over 16s: assessment and management' has acknowledged the widespread use of image-guided facet joint injections with steroid despite the current body of evidence.[25] The evidence for their use will be discussed further in Chapter 2.

The use of steroids in intra-articular injections stems from the rationale that they can reduce inflammation;[66] particulate corticosteroids such as methylprednisolone and triamcinolone are commonly used for lumbar facet joint injections. One randomised controlled trial of sixty subjects demonstrated that steroids were 'effective' in the treatment of LBP, whether administered systemically or via intra-articular injection; this study however was not placebo-controlled (and therefore any improvement due to the natural progression of LBP could not be ruled out), and no invasive diagnostic test for pain of facet joint origin was used.[67] Local anaesthetics have also been shown to have anti-inflammatory effects, and have long-term effectiveness following nerve blocks.[68] It is considered usual practice in the United Kingdom to inject the steroid and local anaesthetic into the joint at the same time.[64]

There is at present no agreed technique for lumbar facet joint injections. One research group in the United Kingdom used a consensus conference process to develop a protocol for therapeutic facet joint injections for a randomised controlled trial.[64] The injections were to be carried out in the prone position with no intravenous sedation, under x-ray imaging without radio-opaque contrast to visualise the joint and confirm needle entry into the joint cleft. A total of 7.5mg bupivacaine and 20mg methylprednisolone would be injected via pre-filled syringes (2ml total volume per joint), and a maximum of six facet joints injected at the L3/4, L4/5 and L5/S1 spinal levels bilaterally. An 'oblique needle technique' has also been described in the literature, with the patient placed in an oblique prone position, typically around 60° for optimal visualisation of the lower lumbar facet joints, with no more than 2ml injected into the joint capsule to avoid capsule rupture and extravasation.[69]

Lumbar facet medial branch nerves can be injected with local anaesthetic as part of the diagnostic procedure to confirm facet joint pain, or as a therapeutic procedure often with local anaesthetic and steroid. The Spine Intervention Society, formerly known as the International Spine Intervention Society, has developed practice guidelines including a step-by-step needle placement technique for this procedure.[70] An oblique approach is used and the target points identified using C-arm fluoroscopy, at the junction of the superior articular process and the transverse process, halfway between the superior border of the transverse process and the mamillo-accessory notch. Confirmation of correct needle placement on the target nerve in the postero-anterior view is required prior to injection of radio-opaque medium to exclude intravascular spread, followed by injection of 0.5ml of local anaesthetic.

Therapeutic lumbar facet joint nerve blocks have however in the past been overlooked in clinical guidelines despite their potential to relieve LBP of facet joint origin.[71] Manchikanti and colleagues reviewed two high quality randomised controlled trials and one moderate to high quality randomised controlled trial of therapeutic nerve blocks and concluded that there was level II evidence for their use in the lumbar spine.[68] Both Falco *et al.* and Datta *et al.* found moderate evidence for their use in the treatment of chronic LBP in their systematic reviews.[72, 73]

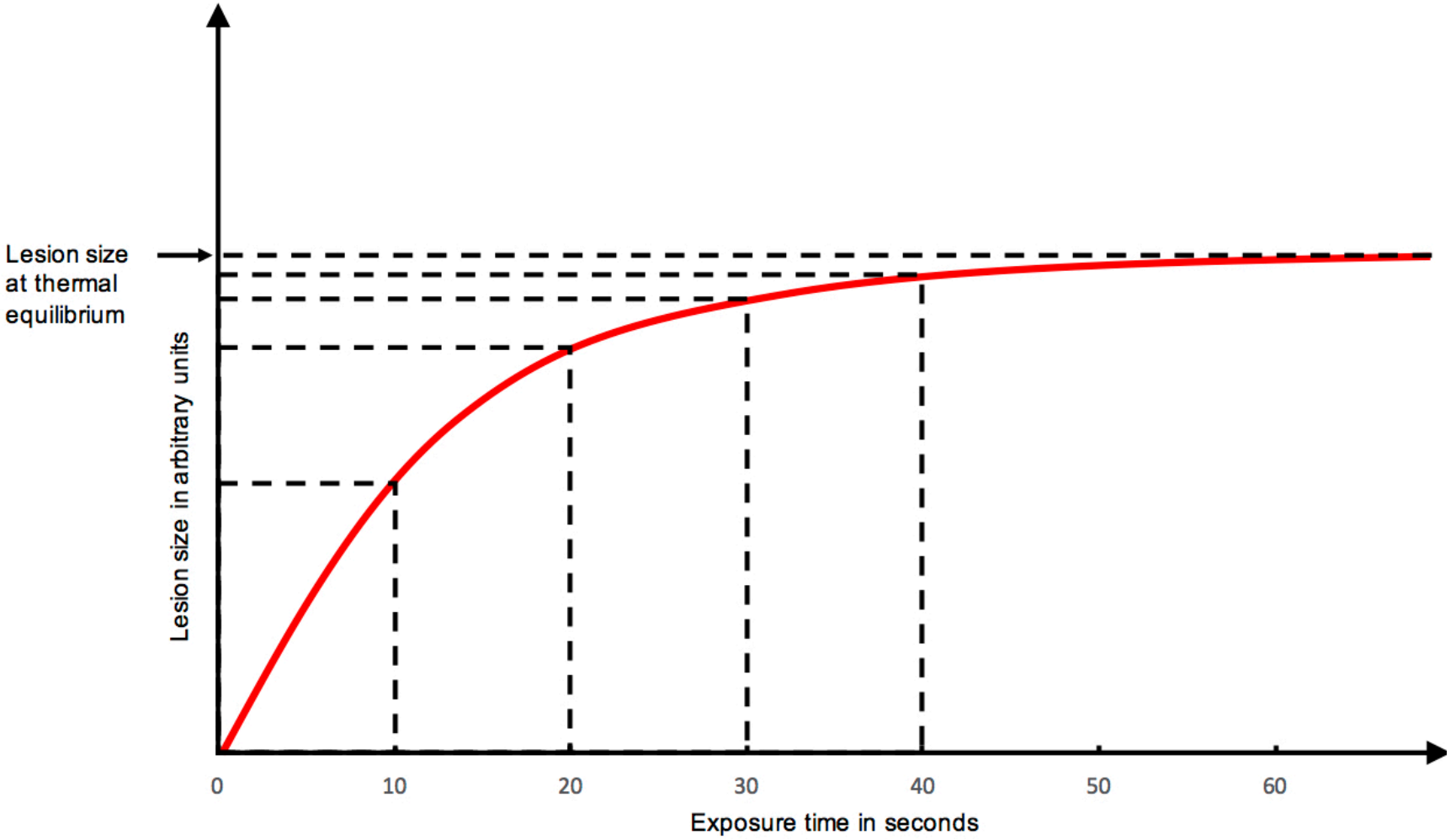
Radiofrequency denervation creates a well-circumscribed lesion at the target site, via the placement of a thermocouple probe inserted through an insulated radiofrequency cannula with an exposed tip. One method described by Gauci recommends placing the cannula in close proximity to the target (the lumbar facet medial branch nerve), and using sensory stimulation at a frequency of 50Hz and the lowest possible voltage to locate the nerve.[74] A low frequency of 2Hz is then applied to rule out motor nerve involvement. A radiofrequency current of approximately 300Hz can then be passed through the probe, generating heat within the surrounding tissues and denaturing the target nerve. The lesion size has been shown to increase with time initially in a linear fashion, before reaching a steady state (see figure 7).

The updated Cochrane review 'Radiofrequency denervation for chronic low back pain' published in 2015 concluded that there was very low to moderate quality evidence for the use of radiofrequency denervation in providing pain relief or improving function, and that there was a lack of high-quality trials, based on a review of 23 randomised controlled trials.[75] The current NICE guidelines in the United Kingdom for managing pain of lumbar facet joint origin however reviewed eight randomised controlled trials and recommend radiofrequency denervation of the medial branch nerves as a cost-effective way of managing moderate to severe chronic LBP when non-surgical treatment has not helped, after a positive response to a diagnostic medial branch block.[25]

At the time of writing, there however remains conflicting advice on the use of radiofrequency denervation in the management of chronic LBP. Lee and colleagues carried out a meta-analysis of seven randomised controlled trials (454 patients) of patients undergoing radiofrequency denervation compared with control procedures; they concluded that the radiofrequency group had less LBP after one year, with the best response seen in those who had a positive result following a diagnostic block.[76] In contrast, the Mint study concluded that there was no evidence to support the use of radiofrequency denervation in addition to a 3-month standardised exercise programme with psychological support for participants with pain of facet joint origin, sacroiliac joint origin, or originating from the intervertebral discs.[77]

The Mint study was a Dutch multicentre non-blinded randomised controlled trial which included 251 participants in the facet joint arm who had chronic LBP and a positive response to a diagnostic block; no clinically important differences were observed between the intervention group and those who received the exercise programme only. A statement representing twelve medical specialty societies including interventional pain specialists, surgeons and physicians has however rejected the findings, criticising its study design (including the lack of baseline pain and function scores), patient selection (controlled diagnostic blocks were not used), injection techniques and data analysis.[78] Provenzano and colleagues also described methodological flaws, which they suggested were due to educational gaps within the interventional pain community.[79] Another critical review by Kuijk and colleagues has concluded that patient selection and recruitment were suboptimal, the interventional pain techniques were not standardised, and the conclusions were erroneous due to inaccurate presentation and misinterpretation of the results.[80]

Figure 7. Plot of lesion size versus exposure time to radiofrequency current. Adapted from Gauci's manual of RF techniques (2008)[74]



Conservative management

Conservative management of LBP is non-invasive and includes pharmacological and non-pharmacological interventions. The latter group can be further categorised into combined physical exercise and psychological treatments (cognitive behavioural therapy and interdisciplinary rehabilitation), physical exercise therapy (such as stretching and yoga), manual therapy (including spinal manipulation and acupuncture), and information and education. One systematic review has shown that these treatments are cost-effective options in the management of LBP.[81]

The 2009 NICE clinical guideline 88 'Early management of persistent non-specific low back pain', which has since been superseded, recommended consideration for referral for a combined physical and psychological programme of around 100 hours over a maximum of eight weeks to those who had no satisfactory improvement after an exercise programme, a course of manual therapy, or acupuncture, and with high disability or significant psychological distress.[26] The National Spinal Taskforce's report 'Commissioning spinal services – getting the service back on track' published in 2013 had identified that a combined physical and psychological programme was the most serious gap in current services in the United Kingdom.[82] The updated NICE guideline NG59 'Low back pain and sciatica in over 16s: assessment and management' again recommended a combined physical and psychological programme with a cognitive behavioural approach, when previous treatments had not been effective and where 'significant psychosocial obstacles' were identified.[25]

Lamb and colleagues carried out a definitive large-scale randomised controlled trial of a cognitive behavioural approach that could be delivered in fewer hours than recommended in the NICE clinical guideline 88.[83] Registered health professionals would receive 2 days' training to deliver the group-based Back Skills Training (BeST) programme, which the research group had demonstrated to show long-term effectiveness and cost-effectiveness in managing subacute and chronic LBP. The training would be provided on-line to allow trainers to

deliver an individual session of 60 minutes, followed by six group sessions lasting 90 minutes each.[84]

The latest evidence from a systematic review for the American College of Physicians clinical practice guideline for LBP has concluded that nonsteroidal anti-inflammatory drugs (NSAIDs) had smaller benefits than placebo for LBP than previously observed, and that duloxetine (a serotonin and noradrenaline reuptake inhibitor) had some benefit in chronic LBP management.[85] The recent American College of Physicians clinical practice guidelines published in 2017 emphasise the use of non-pharmacological treatments such as superficial heat and massage, and recommend NSAIDs as first-line therapy where non-pharmacological therapy has failed, followed by tramadol or duloxetine as second-line therapy. Opioids were only to be considered after an informed discussion where the potential benefits were perceived to outweigh the risks.[86]

Outcomes for chronic pain trials

Effective comparison of outcome assessments between clinical trials require comparable outcome measures. Kaiser and colleagues reviewed core outcome measures recommended for use in trials of chronic pain in general, and for studies of non-specific LBP.[87] This review group noted that there were overlaps in the recommended core domains but also commented on potential gaps between the recommendations, most significantly in psychometric tests of emotional functioning and emotional wellbeing.

Deyo and colleagues proposed certain outcome measures for trials of chronic LBP, later approved by the National Institutes of Health (NIH) Pain Consortium in the United States, with the aim of standardising these measurements across clinical trials.[88] They have advised that clinical researchers use measurement tools with a greater degree of precision than those used in routine clinical practice (see table 3). Bombardier has also proposed core outcome domains for trials of chronic LBP, based on a non-formal consensus process. These

include back-specific function, generic health status, pain, work disability, and patient satisfaction.[89]

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) have recommended core outcome measures that should be considered for clinical trials of chronic pain treatment efficacy and effectiveness, based on consensus from experts in the field of chronic pain treatment outcomes.[90, 91] The six core outcome domains are pain, physical functioning, emotional functioning, participant ratings of global improvement and satisfaction with treatment, symptoms and adverse events, and participant disposition. Specific measures were also recommended for each core outcome domain, for example an 11-point numerical rating scale of pain intensity, and the use of rescue analgesics during the course of the trial.

Table 3. Proposed outcome measures for clinical trials of chronic low back pain. Adapted from Deyo *et al.*'s 'Outcome measures for low back pain research: a proposal for standardized use' (1998)[88]

Domain	Specific instrument
Pain symptoms	Bothersomeness or severity and frequency of LBP and leg pain
Back-related function	Roland Morris Disability Questionnaire[92] (or adaptations), or Oswestry Low Back Pain Disability Questionnaire[93] (or adaptations)
Generic well-being	SF-12[94] (12-Item Short Form Health Survey) or EuroQol instrument for utility-weighted health status;[95] also, "If you had to spend the rest of your life with the symptoms you have right now, how would you feel about it?"
Disability (social role)	Days of work absenteeism, cut down activities, bed rest
Satisfaction with care	Single question on overall satisfaction (optional)

Is new evidence needed to support the use of lumbar facet joint injections? The FACET feasibility study

NICE guideline 88, which covered the early treatment and management of persistent LBP, had acknowledged that there is some evidence from case studies that intra-articular lumbar facet joint injections in the management of persistent LBP may be effective, but insufficient evidence from randomised controlled trials to support their use.[26] In order to provide further high quality evidence, the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme issued a commissioning brief in 2011 to answer the research question, 'Is a definitive study to assess the effectiveness and cost-effectiveness of facet joint injections compared to best non-invasive care for people with persistent non-specific low back pain feasible?'. The commissioning brief stated that the control or comparator should be:

'(i) usual care, as defined by NICE guidelines,
(ii) sham facet joint injection (method of delivering the sham procedure to be investigated in the feasibility phase).'[96]

Two teams were funded by NIHR in response to this commissioned call with different trial designs as requested by the funder; one team explored the addition of intra-articular facet joint injections to best usual non-invasive care (Facet Feasibility, HTA 11/31/01),[97, 98] and the other was a multicentre double-blind randomised controlled trial comparing intra-articular lumbar facet joint injections to a sham procedure, followed by a combined physical and psychological programme (FACET feasibility study, HTA 11/31/02).[96, 99] The FACET feasibility study is explored in detail in this thesis, and the different approaches to trial design by the study teams is discussed further in chapter 5.

There are currently no published, standardised, validated sham procedures for lumbar facet joint injections, or consensus on what would constitute a suitable sham procedure. Vekaria and colleagues defined a sham procedure as one where the participants believed that steroid had been injected into the facet joints, for example when a needle is inserted into the joint but no substance

injected, although the steroid may be injected elsewhere. This group defined a placebo as an inactive or insert substance such as normal saline being injected into or around the joint.[100] One prospective triple crossover study in patients with chronic LBP utilised a sham technique where the needle was positioned outside the facet joint without any substance injected, to avoid irritation of the joint capsule; the other two groups received volume injections with a local anaesthetic and normal saline respectively.[69] Previous controlled trials had used volume injections only, such as one carried out by Lilius *et al.* which compared intra-articular steroid injections with peri-capsular steroid injections and intra-articular saline injections.[36]

The current international and national guidelines do not recommend intra-articular lumbar facet joint injections with therapeutic substances for LBP management, despite their widespread use and potential to relieve LBP and aid rehabilitation. Some practitioners routinely carry out intra-articular facet joint injections of steroid with or without local anaesthetic, whilst others regard these injections as only of diagnostic or short-term value, preferring instead denervation of the facet joint by an ablative treatment modality (radiofrequency denervation) with the aim of achieving longer-term improvement. Further confusion and uncertainty arise from the different approaches to the diagnosis and management of suspected facet joint disease.

The next chapter will identify and critically appraise the existing literature on lumbar facet joint injections for chronic LBP management, and will assess the need to carry out a new or updated systematic review and meta-analysis.

Chapter 2: An overview of systematic reviews and meta-analyses of therapeutic lumbar facet joint injections

Introduction

Systematic reviews in interventional pain management are considered to be essential not only for improving clinical care, but also in policy making and the development of clinical practice guidelines.[101] Systematic reviews have in the past been criticised for their failure to address real-world healthcare decisions; the AHRQ's publication 'Method guide for effectiveness and comparative effectiveness reviews' recommend that study characteristics should be relevant and applicable to the population of interest.[102] The Cochrane handbook defines a systematic review as a way of answering a specific research question by collating all empirical evidence that fulfils pre-specified eligibility criteria. When systematic methods are applied correctly in the identification, selection, synthesis and summary of studies, the risks of bias are minimised, in order to draw clear conclusions and decisions.[103]

A systematic review consists of key components which must be addressed; these include clearly stating the objectives and eligibility criteria, reproducible methodology, systematic search strategies, an assessment for validity (such as risk of bias), and a systematic presentation of the findings.

The Institute of Medicine in their 2011 publication 'Finding what works in health care: standards for systematic reviews' have recommended steps to minimise bias of study quality, defined as 'the tendency for a study to produce results that depart systematically from the truth'.[104] This involves establishing a review team, user and stakeholder involvement, managing bias in reporting and publication, disclosing conflicts of interest, defining the research topic, and writing a peer-reviewed protocol that is publicly available.

Chapter 1 has identified the need for high quality research evidence in the development of clinical practice guidelines of intra-articular lumbar facet joint injections for the management of chronic LBP. In this chapter, the steps taken to identify the existing systematic reviews and meta-analyses of therapeutic injections for LBP will be outlined, and each review meeting the inclusion criteria will be described in terms of their scope using a systematic approach. The methodological quality of each review will be assessed using a validated checklist.[105] Finally, the possibility of carrying out statistical techniques to combine and summarise data from the current body of evidence will be discussed.

Methods

A protocol with the inclusion criteria was developed prior to the initial literature search, with reference to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines.[106] This structured approach was used to screen for eligible systematic reviews and meta-analyses of randomised controlled trials of adult participants with chronic LBP, undergoing therapeutic intra-articular lumbar facet joint injections. The protocol was not prospectively registered on a database of systematic reviews.

Objective

To identify existing systematic reviews and meta-analyses of randomised controlled trials of intra-articular lumbar facet joint injections for chronic LBP management, to assess their methodological quality.

Eligibility criteria

To be eligible for inclusion, the systematic review must have included an adult population with chronic LBP, undergoing intra-articular lumbar facet joint injections with a therapeutic substance as the main intervention. Articles

reviewing other therapeutic interventional pain procedures such as medial branch nerve blocks, radiofrequency denervation and epidural injections, and of diagnostic accuracy, were included if therapeutic lumbar facet joint injections were reviewed also. All comparators were included for review. The outcomes were not to be limited in the search strategy but were expected to include a reduction in pain intensity and an improvement in functioning. Only systematic review papers of randomised controlled trials and meta-analyses were to be included. Outdated systematic reviews with a published update were excluded. Clinical practice guidelines, which drew solely on the evidence from published systematic reviews, were excluded.

Search strategy

Librarian assistance was sought to develop appropriate search terms to identify relevant studies (see appendix 1 for the detailed search strategies). The databases searched were Medline, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL). Additional studies were to be identified from citation tracking and reviewing the references of identified studies.

The search period included articles published between 1966 and February 2017, without language restrictions. The search was repeated in May 2017, prior to submission of the monograph to the NIHR Journals Library, to ensure that no new systematic reviews had been published in the intervening period.

Two reviewers (Saowarat Snidvongs and Fausto Morell-Ducós) independently screened and assessed the full-text articles for eligibility.

Results

The results of the database searches are shown in table 4, and the PRISMA flow diagram of the different phases of the search is illustrated in figure 8.

The Medline search identified 123 results, with 6 duplicates. These 117 records were screened, and 11 full-text articles were assessed for eligibility. Searching the Embase database identified 144 results, with 10 duplicates. The remaining 134 records were screened, with 10 full-text articles assessed for eligibility. The CENTRAL search identified 163 results of which 33 were systematic reviews. One was screened and assessed for eligibility. The systematic review papers identified using these search methods revealed significant overlap in the lists of retrieved articles, with 122 duplicates when the results from the three databases were combined.

Citation tracking and reference checking of the identified systematic reviews and bibliographies were carried out, identifying a further three papers that met the search criteria.[107-109] No meta-analyses of therapeutic lumbar facet joint injections were identified.

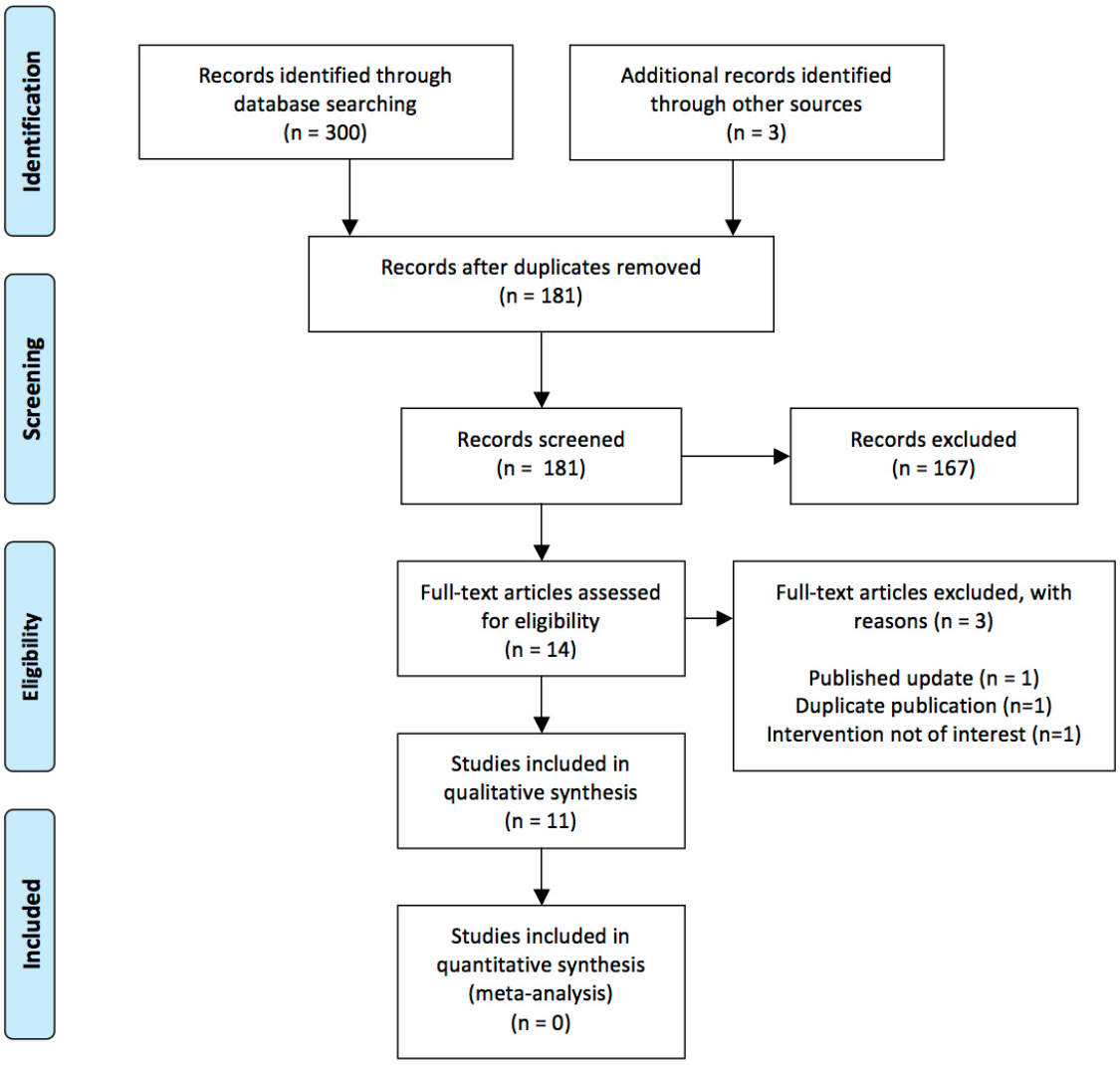
One systematic review paper had a published update and was excluded.[27, 110] It was noted that the Cochrane review had updated a previous review, which had since been withdrawn and was not identified in the databases using the search strategies.[40, 111] The Cochrane review was also published in duplicate in another journal;[112] the duplicate was excluded. Although the systematic review paper published by Falco and colleagues was an update of an earlier systematic review, the reviewers felt that they were sufficiently different in scope and conclusion for both to be included.[72, 73]

One systematic review paper was excluded as it only assessed lumbar facet joint nerve blocks, and not intra-articular injections.[62]

Table 4. Systematic review papers of therapeutic lumbar facet joint injections identified from the database searches

	Slipman *et al.* 2003[107]	Boswell *et al.* 2005[110]	Boswell *et al.* 2007[27]	Staal *et al.* 2008[40]	Staal et al. 2009[112]	Datta *et al.* 2009 [73]	Chou *et al.* 2009 [108]	Henschke *et al.* 2010[109]	Falco *et al.* 2012 [72]	Manchikanti *et al.* Surg Neurol Int 2015[113]	Boswell *et al.* Pain Phys 2015[62]	Manchikanti *et al.* Pain Phys 2015[62]	Vekaria *et al.* 2016[100]	Manchikanti *et al.* World J Orthop 2016[63]
Medline														
Embase														
CENTRAL														
Other sources														
Reasons for exclusion, if applicable		Published update			Duplicate publication						Intervention not of interest			

Figure 8. PRISMA flow diagram depicting the phases of the literature search for systematic reviews and meta-analyses of lumbar facet joint injections for chronic low back pain management[114]



Discussion

Eleven systematic review papers meeting the inclusion criteria were identified from the search. Of these, five included the term 'systematic review' in the title,[27, 68, 100, 109, 113] one paper had the title 'critical review',[107] and another was a 'systematic assessment'.[73] It is however recognised that it is Cochrane policy to not include the terms 'systematic review' or 'meta-analysis' in the title.[103]

The systematic review written by Boswell and colleagues had a potentially misleading title of '..systematic appraisal of the diagnostic accuracy and utility of facet (zygapophysial) joint injections in chronic spinal pain' but only reviewed studies of facet joint nerve blocks and not intra-articular injections.[62]

In 2004, a review of the reporting characteristics of systematic reviews carried out by Moher *et al.* found that 50% of systematic reviews did not include the term 'systematic review' or 'meta-analysis' in the title or abstract,[115] although an update ten years later noted that this proportion had increased to 85% overall, or 94% when Cochrane reviews were omitted.[116] It is recommended in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement that these terms are included in the title, as an informative title improves identification and indexing in databases.[117]

It was not always clear to the reviewers whether some of the reviews were systematic or not, and these papers required further analysis and a consensus discussion. The reviewers referred to the definition of a systematic review as described by Moher and colleagues, where a report was considered to be a systematic review if explicit methods were used, and the objective was clearly stated to summarise evidence from multiple studies.[115]

The scope of the systematic reviews

A structured approach was employed to frame the five components used to develop the research question of each systematic review, as detailed by Liberati *et al.*[117] The components consist of: study population or condition being addressed, the interventions, the comparator, the outcome or study endpoint, and the types of study design included for review. Identification of these components will allow each systematic review to be described in terms of their scope.

Slipman *et al.* Spine, 2003

Slipman and colleagues published 'A critical review of the evidence for the use of zygapophysial injections and radiofrequency denervation in the treatment of low back pain' in 2003, to 'analyse the best studies evaluating various options for lumbar zygapophysial joint syndrome and provide that information to the spine physician community'.[107] The authors did not include the literature search dates. Although systematic methods to identify suitable prospective studies were described, the separate components of the research question were not clearly defined *a priori*; however, the keywords used in the database search indicated that the study population included those with chronic low back, involving the lumbar facet joints. The interventions under review included lumbar facet joint injections and lumbar facet joint radiofrequency denervation. No comparator nor outcomes were specified. The types of study design included in the review were all prospective studies, including randomised controlled trials, a controlled but non-randomised trial, and a case series (of radiofrequency denervation).

Boswell *et al.* Pain Physician, 2007

In 'A systematic review of therapeutic facet joint interventions in chronic spinal pain' Boswell and colleagues carried out an updated systematic review in 2007 to review the effectiveness of therapeutic facet joint interventions for the management of chronic spinal pain of facet joint origin.[27] The initial literature search included papers published between January 1966 and November 2004,

and the updated search reviewed papers published between November 2004 and December 2006. The population was defined in an earlier systematic review from the same group in 2005,[110] to include patients with 'chronic spinal pain' for at least 3 months (but 6 months for studies of radiofrequency denervation), who had received lumbar facet joint injections. Included studies should have had the existence of spinal pain confirmed with, ideally, controlled diagnostic facet joint or nerve blocks, although single block studies would also be considered. This systematic review article also addressed studies of medial branch blocks and radiofrequency denervation. A comparator was not specified. The primary outcome measure was pain relief, and the secondary outcome measures were functional or psychological improvement, return to work, and complications. The reviewers selected randomised controlled trials and also included observational studies, as well as reports of complications.

Staal *et al.* Cochrane Database of Systematic Reviews, 2008

In 2008, Staal and colleagues published an updated Cochrane review, 'Injection therapy for subacute and chronic low-back pain',[40] superseding an earlier 2000 publication which was withdrawn in 2007.[111] The literature search included papers published up until March 2007. The objective was to assess the effectiveness of injection therapy in patients with subacute (lasting 4 weeks or longer) or chronic (lasting over 12 weeks) LBP. Studies of participants aged from 18 to 70 years with LBP of at least one month's duration were considered for inclusion. The intervention was injection therapy for pain relief, including lumbar facet joint injections in addition to epidurals and local site injections. The authors excluded studies of epidural steroids for radicular pain, injections into the intervertebral discs, prolotherapy (injections of irritant substances into a joint), ozone therapy, injections into the sacroiliac joints, and studies where drugs were administered indirectly via a catheter. In contrast to the earlier Cochrane review where homogeneity was not demonstrated between the included studies,[111] the comparators were to be classified according to the therapeutic agent used (steroids or local anaesthetics), and studies were further subdivided into placebo-controlled trials (steroids versus placebo) and trials comparing injections against other treatments. Pain needed to be included as an outcome measure; other outcome measures of importance included a global

measure of improvement, back-specific disability, generic health status or well-being, disability for work, and patient satisfaction. Only randomised controlled trials were included in this review.

Datta *et al*. Pain Physician, 2009

Datta and colleagues presented a systematic review in 2009, 'Systematic assessment of diagnostic accuracy and therapeutic utility of lumbar facet joint interventions' to evaluate the effectiveness of therapeutic lumbar facet joint interventions for the management of chronic LBP of lumbar facet joint origin, and to assess its diagnostic accuracy.[73] The literature search included papers published from 1966 until December 2008. This review group selected from a population of patients with chronic LBP of greater than 3 months' duration, who had achieved at least 80% pain relief following controlled fluoroscopic guided diagnostic blocks (placebo or dual blocks) for the duration of the local anaesthetic used, and improved functional ability. The interventions included in the review were intra-articular lumbar facet joint injections, as well as medial branch nerve blocks and radiofrequency denervation. There was no specified comparator. Studies to be included required a primary outcome measure of pain relief, with secondary outcome measures of functional status improvement, psychological status improvement, return to work, and opioid intake. Certain study designs were excluded, including non-clinical studies, case reports, book chapters, non-evidence-based guidelines, letters and expert opinions.

Chou *et al.* Spine, 2009

In 2009, Chou and colleagues published 'Nonsurgical interventional therapies for low back pain: a review of the evidence for an American Pain Society clinical practice guideline'[108] as part of a larger evidence review to evaluate and guide management of LBP, commissioned by the American Pain Society.[71] The included databases were searched until July 2008. The population was selected from non-pregnant adults aged over 18, with LBP of any duration, alone or with leg pain. Fourteen interventions were chosen for review by an expert panel of the American Pain Society, which were further grouped into four categories. Facet joint injections (defined as 'injection of corticosteroid into the

facet joints') were grouped into the 'intraspinal steroid injections' category; the other categories to be assessed were 'injections outside the spine', 'radiofrequency denervation and related procedures', and 'spinal cord stimulation'. No comparator was specified. The outcome measures included back-specific function, generic health status, pain, work disability, and patient satisfaction. Only randomised controlled trials and systematic reviews were included. Studies of intra-articular facet joint injections and therapeutic medial branch blocks were grouped together in the discussion.

Henschke *et al.* European Spine Journal, 2010

Henschke and colleagues carried out a systematic review in 2010, 'Injection therapy and denervation procedures for chronic low-back pain: a systematic review' to evaluate the current evidence for injections into and outside the spine for non-specific chronic LBP management.[109] The literature search was carried out until November 2009. Studies were selected to include adult participants with chronic LBP, defined as pain persisting for over 12 weeks' duration, including radiculopathy. Randomised controlled trials of non-specific degenerative pathology such as osteoarthritis were included, but studies of pathological conditions (for example ankylosing spondylosis or spinal stenosis) were excluded. The interventions to be assessed were injections of medications or proteolytic enzymes, and radiofrequency or thermal denervation procedures, into predefined anatomical sites for LBP, specifically facet joints, intervertebral discs, and spinal nerves. There was no comparator. The primary outcome measures were pain and functional status; outcome measures should include at least one of: pain intensity, back-specific functional status, perceived recovery, and return to work. Only randomised controlled trials were considered for review.

Falco *et al.* Pain Physician, 2012

Falco and colleagues noted that previously published systematic reviews of spinal injections for chronic LBP management such as the American Pain Society's evidenced-based clinical practice guidelines and the Cochrane review reported conflicting conclusions.[40, 108] The literature search dates were from

database inception until June 2012. In 2012, this group published 'An update of the effectiveness of therapeutic lumbar facet joint interventions', updating a previous systematic review[73] to determine the effectiveness of lumbar facet joint interventions.[72] Studies to be included for review were of adult participants with 'chronic lumbar facet joint pain' of at least 3 months' duration, and participants should have failed previous treatments such as pharmacotherapy or exercise therapy prior to receiving an interventional pain procedure. The interventions reviewed were lumbar facet joint interventions (further subdivided into radiofrequency neurotomy, facet joint nerve blocks, and intra-articular injections) carried out under fluoroscopic, CT or MRI guidance. Studies were excluded if they had been performed blind or under ultrasound imaging. A comparator was not described. The primary outcome measure was pain relief, and the secondary outcome measures included functional improvement, change in psychological status, return to work, opioid reduction, other drugs, other interventions, and complications. Randomised controlled trials were included, alongside non-randomised observational studies and case reports and reviews for adverse events.

Manchikanti *et al.* Surgical Neurological International, 2015

In 2015, Manchikanti and colleagues carried out a systematic review 'Comparison of the efficacy of saline, local anesthetics, and steroids in epidural and facet joint injections for the management of spinal pain: A systematic review of randomized controlled trials' published in *Surgical Neurological International* to describe the role of saline and local anaesthetics in epidural and facet joint injections, and to compare their long-term effects with steroid.[113] The literature search included papers published from 1966 until March 2014. The population was not clearly defined *a priori* but included studies of patients with LBP of at least 3 months' duration. The interventions to be assessed were epidurals (via caudal, interlaminar and transforaminal routes), facet joint injections, and nerve blocks, in the cervical, thoracic and lumbar regions. As a comparator, studies to be included for review required a true active control design, where substances were injected into the same area to compare two difference procedures or drugs. True placebo study designs, with injections of inactive solutions into inactive structures, were excluded. The primary outcome

measure was pain relief, and the secondary outcome measure was functional improvement. This systematic review only included randomised active or placebo controlled trials.

Manchikanti *et al.* Pain Physician, 2015

In the same year, Manchikanti and colleagues also published a systematic review in *Pain Physician, '*A systematic review and best evidence synthesis of the effectiveness of therapeutic facet joint interventions in managing chronic spinal pain', with an aim of assessing the effectiveness of therapeutic facet joint injections with 'appropriate methodology'.[68] The literature search period was between 1966 and March 2015. The population to be reviewed had pain in the neck, mid-back, upper back and low back for at least 3 months; studies were excluded if the pain was due to acute trauma, fractures, malignancy or inflammatory diseases. The review included studies of cervical, thoracic and lumbar facet joint interventions with 'proper technique' under fluoroscopic, CT or MRI guidance. No comparator was specified *a priori*. The primary outcome measure was pain relief, and the secondary outcome measure was functional status improvement. Randomised controlled trials and observational studies were included for review.

Vekaria *et al.* European Spine Journal, 2016

Vekaria and colleagues published a systematic review in 2016 of randomised controlled trials of therapeutic lumbar facet joint injections, 'Intra-articular facet joint injections for low back pain: a systematic review'.[100] The literature search included papers published from database inception through April 2015. The authors reviewed studies of adult participants reporting LBP, which were further subdivided into acute (less than six weeks), sub-acute (six to twelve weeks) and chronic (over twelve weeks) categories. The interventions were injections into or around the facet joints. The comparators included a sham procedure (a needle or device is inserted into the facet joint but no substance injected, to make the participant believe that the active drug had been injected), placebo injection (an inactive substance such as saline is injected into or around the facet joint) or conservative therapy. The conservative therapies used as

comparators included medications, steroid injections into areas other than the facet joints, physical therapies, and psychological interventions. The primary outcome measures were symptom relief based on pain and back-specific functional status, and the secondary outcome measure was adverse events. Only randomised controlled trials were included for review.

Manchikanti *et al*. World Journal of Orthopedics, 2016

In 2016, Manchikanti and colleagues published a further systematic review to assess the therapeutic effectiveness of lumbar facet joint interventions, and also to assess the diagnostic accuracy of lumbar facet joint nerve blocks, 'Management of lumbar zygapophysial (facet) joint pain'.[63] The literature search dates were between 1966 and March 2015. Studies of patients over 18 years of age with 'chronic lumbar facet joint pain' of at least 3 months' duration were considered for review; to be included, patients must have additionally failed previous pharmacotherapy, physical therapy and exercise therapy. The interventions to be assessed included 'multiple interventional techniques' and were not clearly defined *a priori*; amongst the therapeutic interventions, studies of radiofrequency denervation, lumbar facet joint nerve blocks and lumbar intra-articular injections were included. A comparator was not specified. The primary outcome measure for efficacy studies was pain relief, and the secondary outcome measure was functional improvement. Randomised controlled trials of efficacy in managing lumbar facet joint pain were included.

Is there heterogeneity between the scopes of the systematic reviews?

Population

All the systematic reviews identified included studies of adult patients with chronic LBP of at least three months' or twelve weeks' duration, although Staal *et al.* also reviewed patients with pain for at least one month, with subacute pain defined as pain lasting for four weeks or longer.[40] Similarly, Vekaria *et al.* included studies of acute (under six weeks' duration) and sub-acute (six to twelve weeks) LBP.[100]

Falco *et al.* and Manchikanti *et al.* (in *World Journal of Orthopedics*) only included studies where patients had failed previous non-interventional treatments such as pharmacotherapy or physical therapy.[63, 72]

The majority of the systematic reviews did not specify how the diagnosis of pain originating from the lumbar facet joints was reached; however, Datta *et al.* only included studies in which patients had already received controlled (placebo or dual, with comparative local anaesthetics) diagnostic medial branch nerve blocks and obtained at least 80% pain relief and functional improvement.[73] Boswell *et al.* accepted single diagnostic blocks too, as the authors acknowledged that studies with dual blocks were scarce.[27] Falco *et al.* and Manchikanti *et al.* (in *Pain Physician*) excluded reports 'without appropriate diagnosis' although it was not clear what this involved.[68, 72]

Interventions

All the systematic reviews included interventional studies of intra-articular lumbar facet joint injections; Vekaria *et al.* accepted studies of injections around the facet joints (peri-articular) also.[100] The active drugs discussed in the reviews included steroids, local anaesthetics, and sodium hyaluronate.[34] Henschke *et al.* also considered studies of proteolytic enzymes (chemonucleolysis).[109] Manchikanti *et al.* (in *Surgery Neurological International*) only included randomised controlled trials with saline, local anaesthetic and/or steroid.[113]

In addition to reviewing studies of intra-articular lumbar facet joint injections, the majority of the systematic reviews identified from the searches also assessed studies of medial branch nerve blocks,[27, 40, 63, 68, 72, 73, 109, 113] as well as studies of radiofrequency denervation.[27, 40, 63, 68, 72, 73, 109] Staal *et al*. and Manchikanti *et al.* (in *Surgery Neurological International*) additionally reviewed studies of epidurals and local site injections.[40, 113] Chou *et al.* reviewed 14 'nonsurgical interventional therapies' for LBP, as chosen by an expert panel from the American Pain Society.[108]

Three systematic reviews included studies of interventions at all spinal levels (cervical, thoracic and lumbar), [27, 68, 113] whereas the other studies included studies involving the lumbar spine only. Datta *et al.* and Manchikanti *et al.* (in *World Journal of Orthopedics*) also included studies of diagnostic accuracy within their scope for review.[63, 73]

Comparator

Many of the systematic reviews did not specify a comparator *a priori*; Staal *et al.* however grouped studies into those of steroids versus placebo, steroids versus other treatments such as Sarapin or a home stretching programme, and local anaesthetics versus other treatments such as steroid.[40] Manchikanti *et al.* (in *Surgery Neurological International*) included only those studies where a true active control design was utilised, specifically trials comparing saline solution, local anaesthetic and steroid.[113]

Outcomes

All the systematic reviews included pain as an important or primary outcome measure. Other outcome measures included in the reviews were disability and functional status improvement, psychological improvement, return to work, patient satisfaction, and a reduction in opioid intake. Some reviews also looked at reports of complications and adverse events.[27, 72, 100]

Study design

All the systematic reviews assessed randomised controlled trials, although Slipman *et al*. included a controlled but non randomised study,[107] and Boswell *et al.,* Falco *et al.* and Manchikanti *et al.* (in *Pain Physician*) also reviewed observational studies.[27, 68, 72]

The different scopes of the systematic reviews

The previous section has demonstrated that no two systematic review papers have the same scope; many differ in the population under review, and in the types of included studies. Most authors did not review one intervention only (intra-articular lumbar facet joint injections) but also reviewed other interventional spinal procedures at other spinal levels.

The different scopes of the systematic reviews allow different yet relevant research questions to be answered and reflect the different scopes of the studies themselves. As demonstrated by several authors including the GDGs of the NICE LBP guidelines and in the Cochrane review,[25, 26, 40] the substantial heterogeneity between the studies meant that reviewers often had to split the studies depending on the agents injected, and whether the comparator was a placebo or sham, or other treatment, in order to carry out any sub-group analyses. This approach could allow for reviews of clinically comparable groups instead of a sub-group containing a single study; however, is clear that there are still differences within the sub-groups, including the entry criteria and use of diagnostic blocks, site of injections, dose of steroid, type of 'usual care', and outcome measures.

Clinical decision making relies on an evidence-based approach, yet the randomised controlled trials of lumbar facet joint injections in chronic LBP management have heterogeneous populations with relatively small sample sizes and varying entry criteria. Interpretation of these research outcomes may be challenging, and decision-makers should not rely on statistically significant differences alone, as the results also need to be clinically meaningful. Any evidence statements from the systematic reviews therefore need to be interpreted with caution; is not possible to support or refute the use of spinal injections based on the current evidence.

Assessing the methodological quality of systematic reviews: AMSTAR checklist

A measurement tool for the 'Assessment of Multiple Systematic Reviews' (AMSTAR) was developed in response to a perceived need for a new instrument to assess the methodological quality of systematic reviews of randomised controlled trials.[105] Shea and colleagues utilised expert opinion to review the published literature and update previously available tools to create a new 37-item assessment tool, with 11 components in the form of a checklist. Since its publication in 2007, it has been shown to have good inter-rater agreement, test-retest reliability, face and construct validity, and feasibility.[118] As discussed earlier in this chapter, the assessment process examines the likelihood that the review will generate unbiased results; potential types of bias include selection bias, performance bias, attrition bias, detection or measurement bias, and reporting bias.[119]

One debate paper critically appraised the AMSTAR checklist from the point of view of an assessor.[120] The challenges of using this tool were described, and it was noted that some items within the checklist appeared to assess the reporting quality, rather than the methodological quality, of the systematic review. This paper also commented that difficulties in interpretation of some of the questions may lead to heterogeneity of its use, and suggested some solutions to improve its reliability as a measurement tool.

The AMSTAR checklist was used by two reviewers (Saowarat Snidvongs and Fausto Morell-Ducós) to independently assess each systematic review, with reference to the guidance notes on the checklist.[121] A consensus process or third reviewer was to be used if there were any disagreements. Each review paper was scored out a maximum of eleven points, using the on-line calculator.[121] One point was given for each item that scored 'Yes', and no points given for 'No', 'Can't answer' or 'Not applicable'.

'Review of reviews': results of the AMSTAR checklist

A summary table of the AMSTAR checklist scores for each systematic review is shown in table 5.

The reviewers found that item 1 of the checklist, referring to whether an *a priori* or pre-determined research question or inclusion criteria was provided or not, was difficult to answer. Although these were generally well-detailed in most of the systematic reviews, it was usually unclear whether these had been published in advance. Only one group stated that their systematic review had been prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO), with a published protocol.[122, 123]

The majority of the systematic review groups clearly stated that there were at least 2 independent reviewers selecting the studies for inclusion, and for carrying out the data extraction. Most groups described a consensus process in place for disagreements (item 2). A comprehensive literature search was performed by most review groups, including at least two electronic sources (usually Medline, Embase and CENTRAL) as well as additional strategies and resources, ranging from trial registries and conference abstracts to consulting known experts in the field (item 3). However, most authors did not specifically indicate that they also searched for grey or unpublished literature (item 4).

Most of the systematic review papers included a list of included and excluded studies (item 5). However, it was unclear to the reviewers whether the excluded studies were from the first phase of the search, where the titles and abstracts are evaluated from a larger pool of papers, or from the second phase, where the full text articles were assessed. In the consensus discussion, it was decided to accept a list of excluded papers from the second stage only, as it would not always be possible to list all the excluded papers from the first stage evaluation. Faggion's critical appraisal also called for improved clarity on this item.[120]

The characteristics of included studies were sufficiently described by most of the authors, either in table format or in the body of the text (item 6). Similarly,

the majority of authors discussed *a priori* methods of assessing the scientific quality of the included studies (item 7) and applied these correctly when formulating conclusions (item 8). None of the authors were able to combine the findings of the included studies, and many described heterogeneities within the study population which precluded any data synthesis (item 9).

Only two papers (Henscke *et al.* 2010 and Vekaria *et al.* 2016) discussed the possibility of publication bias, although both groups commented on the small numbers of published trials without a positive effect, reducing the likelihood of publication bias (item 10).[100, 109]

The reviewers were unable to score 'Yes' on item 11 of the AMSTAR checklist for any of the systematic review papers. This item related to whether conflicts of interest were included; the guidance notes state that this should include the source of funding or support for the included studies too, and not only for the systematic review. None of the systematic reviews mentioned sources of funding for the included studies; this item was included by the AMSTAR authors as there is evidence that industry-sponsored studies may favour sponsored products.[124] As this would not be detected as a design or methodology flaw, reporting this would improve confidence in the findings of the review.

Of the eleven systematic review papers scored, it can be seen that no paper achieved 'Yes' on all eleven items. Vekaria *et al.* had the highest score of 10/11 but like the other papers, did not declare sources of funding or support for the included studies.[100] Datta *et al.* had the lowest score of 2/11, in part due to its strict inclusion criteria and no included studies, so that many items on the checklist were not applicable.[73]

Table 5. AMSTAR checklist scores for each systematic review. Yes (Y) = green, No (N) = red, Can't answer (CA) = yellow, Not applicable (NA) = blue

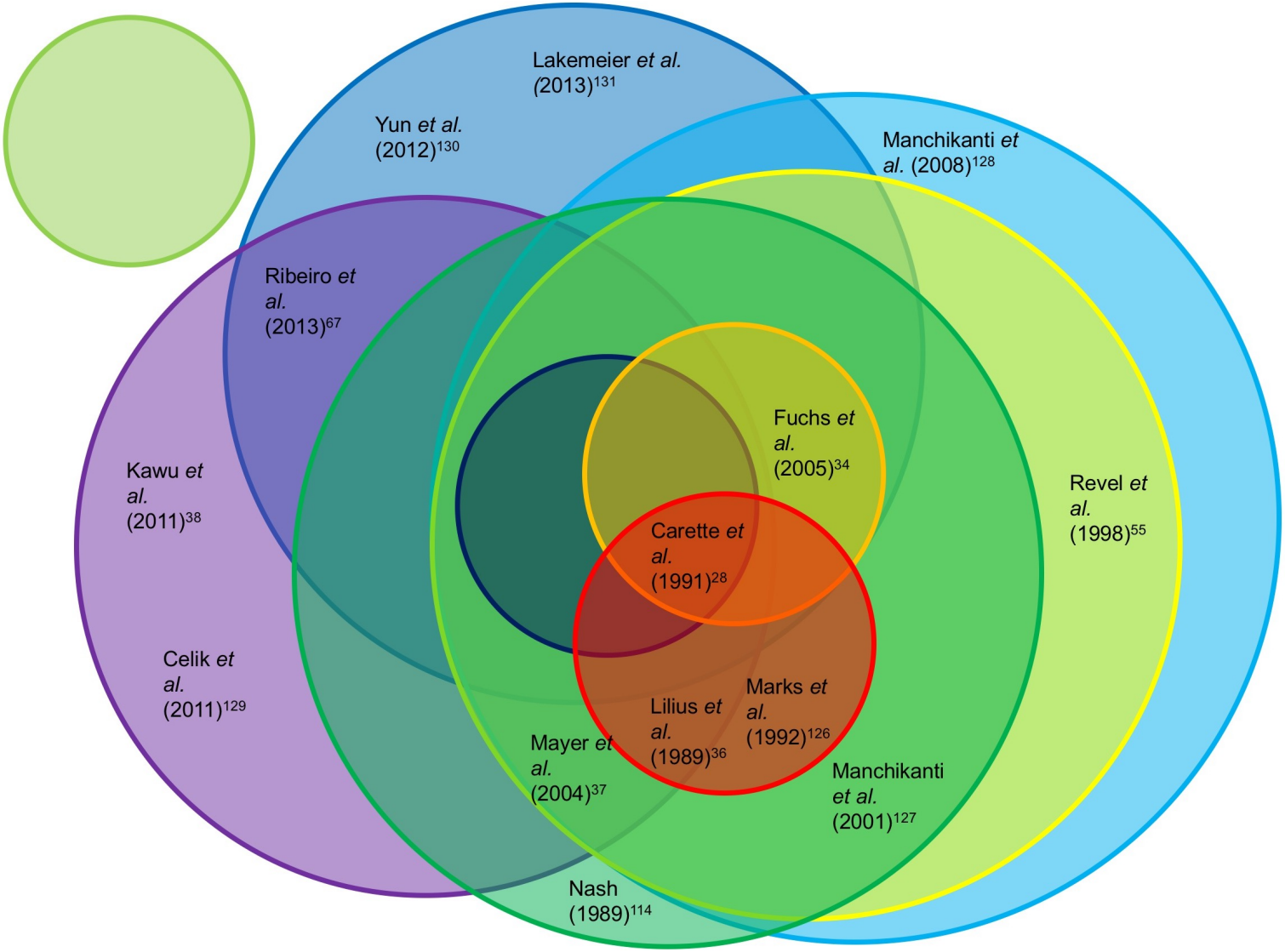
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	AMSTAR score /11
Slipman *et al.* 2003[107]	CA	CA	N	N	Y	Y	Y	Y	CA	N	CA	4
Boswell *et al.* 2007[27]	CA	CA	Y	CA	Y	Y	Y	Y	CA	N	CA	5
Staal *et al.* 2008[40]	Y	Y	Y	N	Y	Y	Y	Y	Y	N	CA	8
Datta *et al.* 2009[73]	CA	CA	Y	CA	Y	NA	NA	NA	NA	N	CA	2
Chou *et al.* 2009[108]	CA	Y	Y	Y	Y	N	Y	Y	N	N	CA	6
Henschke *et al.* 2010[109]	CA	CA	N	N	Y	Y	Y	Y	Y	Y	N	6
Falco *et al.* 2012[72]	CA	Y	Y	CA	Y	Y	Y	Y	Y	N	CA	7
Manchikanti *et al.* Surg Neurol Int 2015[113]	CA	Y	Y	CA	Y	Y	Y	Y	Y	N	N	7
Manchikanti *et al.* Pain Phys 2015[68]	CA	Y	Y	CA	N	Y	Y	Y	Y	N	CA	6
Vekaria *et al.* 2016[100]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CA	10
Manchikanti *et al.* World J Orthop 2016[63]	CA	Y	Y	CA	N	Y	Y	Y	N	N	CA	5

Randomised controlled trials included in the best evidence synthesis

The eleven systematic review papers identified a total of fourteen randomised controlled trials between them. The Venn diagram below illustrates that given the variation in dates when reviews were undertaken and their precise inclusion/exclusion criteria, no one review included all these trials (see figure 9). Full-text versions of all but one trial were retrieved.[125] These thirteen randomised controlled trials are summarised in table 6.

Figure 9. Randomised controlled trials included in each systematic review

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]



Systematic review paper	
Slipman *et al.* 2003[107]	
Boswell *et al.* 2007[27] Falco *et al.* 2012[72]	
Staal *et al.* 2008[40]	
Datta *et al.* 2009[73]	
Chou *et al.* 2009[108]	
Henschke *et al.* 2010[109]	
Manchikanti *et al.* 2015 Pain Physician[68] Manchikanti *et al.* 2016 World J Orthop[63]	
Manchikanti *et al.* 2015 Surg Neurol Int[113]	
Vekaria *et al.* 2016[100]	

Table 6. Randomised controlled trials of efficacy of therapeutic facet joint injections identified from previous systematic reviews. Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

First author, year (country, n randomised)	Population	Intervention	Comparator	Primary outcome	Follow-up	Key findings
Lilius, 1989 (Finland, n=109)[36]	Unilateral LBP >3 months, failed analgesics and physiotherapy No diagnostic blocks	1. X-ray guided intra-articular lumbar facet joint injections with bupivacaine and methylprednisolone 2. X-ray guided pericapsular injections with bupivacaine and methylprednisolone	Sham (x-ray guided intra-articular lumbar facet joint injections with physiological saline)	Not stated – assessed pain, disability and return to work	3 months	No difference in outcomes at follow-up between 2 active groups and sham Improvement in pain, disability and work attendance in all groups

First author, year (country, n randomised)	Population	Intervention	Comparator	Primary outcome	Follow-up	Key findings
Carette, 1991 (Canada, n=101)[28]	LBP >6 months, normal neurological examination >50% pain reduction after single intra-articular diagnostic injections with lidocaine	Fluoroscopic guided intra-articular lumbar facet joint injections with methylprednisolone and isotonic saline	Sham (fluoroscopic guided intra-articular lumbar facet joint injections with isotonic saline)	Not stated – assessed pain severity, back mobility, and limitation of function	6 months	No differences in outcomes at 1 and 3 months between the 2 groups At 6 months, patients in the intervention group reported more self-rated improvement, less pain intensity, and less physical disability than the sham group
Marks, 1992 (Scotland, UK, n=86)[126]	LBP >6 months, failed non-narcotic	X-ray guided intra-articular lumbar facet joint injections with	X-ray guided lumbar facet joint medial branch nerve blocks	Pain intensity	3 months	Marginally longer duration of response in

First author, year (country, n randomised)	Population	Intervention	Comparator	Primary outcome	Follow-up	Key findings
	analgesics and physiotherapy No diagnostic blocks	lidocaine and methylprednisolone	with lidocaine and methylprednisolone			the intervention group after 1 month, otherwise no difference in outcomes at other time points between the 2 groups Some short-term pain relief seen in both groups
Revel, 1998 (France, n=80)[55]	LBP >3 months, failed analgesics and physical therapy	Fluoroscopic guided intra-articular lumbar facet joint injections with lidocaine, + peri-articular corticosteroid	Fluoroscopic guided intra-articular lumbar facet joint injections with saline, + peri-articular corticosteroid steroid	Pain intensity using VAS	30 minutes after injections	Significantly reduced pain scores in the intervention group compared

First author, year (country, n randomised)	Population	Intervention	Comparator	Primary outcome	Follow-up	Key findings
	No diagnostic blocks	steroid injection (not evaluated)	injection (not evaluated)			to the comparator
Manchikanti, 2001 (US, N=84)[127]	LBP >6 months, failed conservative management Positive response following controlled comparative diagnostic blocks with lidocaine and bupivacaine	Lumbar facet medial branch nerve blocks with lidocaine or bupivacaine, Sarapin and methylprednisolone	Lumbar facet medial branch nerve blocks with lidocaine or bupivacaine, and Sarapin	Not stated – assessed pain characteristics, physical health, mental health, functional status, return to work, and narcotic intake	Up to 2.5 years	No difference in outcomes at follow-up between the groups, improvement in pain and functional outcomes in both groups
Mayer, 2004 (US, n=70)[37]	'Chronic disabling work	Fluoroscopic guided bilateral intra-articular			Not specified –	No difference in pain and

First author, year (country, n randomised)	Population	Intervention	Comparator	Primary outcome	Follow-up	Key findings
	related lumbar spinal disorder' for >6-12 months, 'lumbar segmental rigidity' on clinical examination No diagnostic blocks	lumbar facet joint injections with lidocaine, bupivacaine and depot corticosteroid, and home stretching exercise programme	Home stretching exercise programme only	Range of motion, pain and disability	after completing the home stretching exercise programme	disability report at follow-up between the 2 groups, greater improvement in range of motion in the intervention group
Fuchs, 2005 (Germany, n=60)[34]	Low back pain >3 months, facet joint osteoarthritis on imaging	CT-guided intra-articular lumbar facet joint injections with triamcinolone	CT-guided intra-articular facet joint injections with sodium hyaluronate	Pain intensity, functioning, and quality of life	180 days	No difference in outcomes at follow-up between the 2 active groups, improvement in pain and functional

First author, year (country, n randomised)	Population	Intervention	Comparator	Primary outcome	Follow-up	Key findings
						outcomes in both groups
Manchikanti, 2008 (US, n=120)[128]	LBP >6 months, failed conservative management 80% pain relief following controlled comparative diagnostic blocks with lidocaine and bupivacaine	IA. Lumbar facet joint medial branch nerve blocks with bupivacaine IB. Lumbar facet joint medial branch nerve blocks with bupivacaine and Sarapin	IIA. Lumbar facet joint medial branch nerve blocks with bupivacaine and steroid IIB. Lumbar facet joint medial branch nerve blocks with bupivacaine, steroid and Sarapin	Not stated – assessed pain relief, work status, opioid intake and functional status	1 year	No difference in outcomes at follow-up between the groups, improvement in pain and functional outcomes in both groups
Kawu, 2011 (Nigeria, n=18)[38]	LBP >3 months, failed analgesics, MRI	X-ray-guided lumbar facet joint injections with bupivacaine and methylprednisolone	Physiotherapy (McKenzie regimen)	Not stated – assessed pain relief and	6 months	Greater decreases in pain in the intervention

First author, year (country, n randomised)	Population	Intervention	Comparator	Primary outcome	Follow-up	Key findings
	features of facet joint arthropathy No diagnostic blocks			satisfaction with treatment		group compared to the comparator, and higher levels of satisfaction
Celik, 2011 (Turkey, n=80)[129]	LBP <4 months No diagnostic blocks	Fluoroscopic guided lumbar facet joint injections with bupivacaine and methylprednisolone	Diclofenac, thiocolchicoside and bed rest for 4 days	Not stated – assessed LBP disability and pain intensity	6 months	Greater decreases in pain and disability in the intervention group compared to the comparator, improvement in pain and functional outcomes in both groups

First author, year (country, n randomised)	Population	Intervention	Comparator	Primary outcome	Follow-up	Key findings
Yun, 2012 (Korea, n=57)[130]	LBP (no duration specified), clinical indicators of facet syndrome No diagnostic blocks	Fluoroscopic guided lumbar facet joint injections with lidocaine and triamcinolone	Ultrasound-guided lumbar facet joint injections with lidocaine and triamcinolone	Pain and activities of daily living	3 months	No difference in outcomes at follow-up between the 2 active groups, improvement in pain and functional outcomes in both groups
Ribeiro, 2013 (Brazil, n=60)[67]	LBP >3 months, clinical diagnosis of lumbar facet joint syndrome No diagnostic blocks	Fluoroscopic guided intra-articular lumbar facet joint injections with lidocaine and triamcinolone	Intramuscular paravertebral injections with lidocaine and triamcinolone	Not stated – assessed quality of life, functional capacity, pain on back extension, % improvement scale, analgesic usage	24 weeks	'Slightly superior' results in the intervention group compared to the comparator, improvement in pain and

First author, year (country, n randomised)	Population	Intervention	Comparator	Primary outcome	Follow-up	Key findings
						functional outcomes in both groups
Lakemeier, 2013 (Germany, n=56)[131]	LBP >24 months >50% pain reduction after single intra-articular diagnostic injection with bupivacaine	Fluoroscopic guided intra-articular lumbar facet joint injections with bupivacaine and betamethasone	Radiofrequency denervation of the lumbar facet joint medial branch nerves	LBP-related disability using Rowland-Morris Questionnaire	6 months	No difference in outcomes at follow-up between the 2 active groups, improvement in pain and functional outcomes in both groups

What is the current evidence for therapeutic lumbar facet joint injections?

Table 7 summarises the best evidence synthesis from each systematic review of randomised controlled trials of therapeutic lumbar facet joint injections for chronic LBP management.

Of the eleven systematic review papers, three concluded that therapeutic lumbar facet joint injections were ineffective,[107, 108, 113] although the systematic review carried out by Manchikanti and colleagues published in *Surgical Neurology International* also included a randomised controlled trial of cervical facet joint injections in the synthesis of evidence. Four reviews found limited to moderate evidence to support their use;[27, 63, 68, 109] Henschke and colleagues however described this evidence to be of low or very low quality. The remaining three systematic reviews did not find sufficient evidence to support the use of lumbar facet joint injections for the treatment of LBP.[40, 72, 100]

It has already been shown earlier in this chapter however that systematic review papers are of variable methodology quality, with AMSTAR scores ranging from 2 to 10 out of a maximum of eleven points. Some systematic review authors have been criticised by other review groups; Van Boxem and colleagues noted that the paper 'Injection therapy and denervation procedures for chronic low-back pain: a systematic review' by Henschke and colleagues[109] did not have any input from a clinical expert in pain management, and inappropriately grouped different pain syndromes together, despite different pathophysiological mechanisms.[132] The same group also criticised the Cochrane review by Staal *et al*., 'Injection therapy for subacute and chronic low-back pain',[40] as they felt that the patient population was too heterogeneous to draw any clinically useful conclusions.[133]

Despite their methodological drawbacks however, none of the authors attempted to pool the results of their findings due to clinical heterogeneity, with most of the systematic review papers opting for a narrative discussion instead. Staal *et al.* subdivided the studies according to the target of injection (such as lumbar facet joints and according to the therapeutic agent that was used (for example steroids or local anaesthetics) with an aim of making the studies more

comparable and clinically relevant.[40] Similarly, Vekaria *et al.* also divided the outcomes into studies which compared lumbar facet joint injections with a sham control, versus a conservative treatment control.[100]

It can be demonstrated that the evidence varies between the systematic reviews, even those analysing the same studies. None of the review groups were able to carry out meta-analyses or data pooling, and any concluding evidence was therefore based on relatively small numbers of randomised controlled trials, with no more than 8 randomised controlled trials of variable quality being reviewed in each systematic review. Some groups also included evidence from observational studies in formulating their conclusions.[27, 68, 72] Designed with an intention to observe and not interfere with routine care, these are associated with a higher risk of bias compared to randomised controlled trials in terms of selection, performance, detection, attrition, and selective outcomes reporting.[134]

Table 7. The evidence for intra-articular lumbar facet joint injections for chronic low back pain management

Systematic review paper	Number of RCTs included in evidence synthesis	Summary of evidence
Slipman *et al.* 2003[107]	3	Level III (moderate) to IV (limited) evidence that therapeutic lumbar facet joint injections are not effective
Boswell *et al.* 2007[27]	2	Moderate evidence for intra-articular lumbar facet joint injections with local anaesthetic and steroid for short- and long-term improvement in LBP
Staal *et al.* 2008[40]	7	No strong evidence to support injection therapy for LBP
Datta *et al.* 2009[73]	0	Level III or limited evidence for therapeutic facet joint interventions
Chou *et al.* 2009[108]	7	Fair evidence that intra-articular facet joint steroid injections are not effective
Henschke *et al.* 2010[109]	8	Low to very low quality evidence to support the use of injection therapy for chronic LBP
Falco *et al*. 2012[72]	2	Limited evidence for intra-articular injections
Manchikanti *et al.* 2015 Surg Neurol Int[113]	2	Level 1 evidence (obtained from high-quality randomised controlled trials of lumbar and cervical facet joint injections) for lack of effectiveness of intra-articular injections
Manchikanti *et al.* 2015 Pain Physician[68]	5	Level 3 (moderate) evidence for lumbar intra-articular injections of steroids
Vekaria *et al*. 2016[100]	6	Insufficient high-quality evidence to support the use of facet joint injections over placebo/sham-controlled procedures or conservative therapy for LBP
Manchikanti *et al.* World J Orthop 2016[63]	5	Level 3 evidence for short-term improvement of 6 months or less for intra-articular lumbar facet joint injections

Is there a need for a new systematic review?

It is generally considered more efficient to update an existing system rather than addressing the same research question with a new protocol, as the updating process will also take previous comments and criticisms into account, to allow for ongoing improvement with time. Garner and colleagues, as panel members for updating guidance for systematic reviews, took part in a workshop organised by Cochrane, a global organisation that aims to promote high quality health research evidence, in order to develop consensus guidance on this process; an updated systematic review was defined by this group as a new edition of a published systematic review with changes that can include new data, new methods, or new analyses compared to the previous edition.[135] A number of steps were recommended by the panel to assess currency, to identify new relevant methods, studies or other information, and to assess the effect of the update i.e. whether any new information will change the findings or credibility.

The possibility of updating an existing systematic review of therapeutic lumbar facet joint injections for non-specific LBP was explored using the decision framework developed by the panel members. The new review would address a current question, as the future for this procedure remains uncertain, due to a lack of consistent, good quality evidence from published randomised controlled trials. The existing systematic reviews have had good access and use (for example, the systematic review published by Vekaria *et al.* in 2016 has been downloaded over 1500 times in its first year of publication).[136] However, the methodological quality of previous reviews has been variable, as quantified using the AMSTAR checklist, and may have generated biased results and conclusions. One recent survey of 250 journals found that approximately half of the systematic reviews were out of date after 5.5 years, and that only one journal gave clear guidance on updating the reviews.[137]

Many existing systematic reviews of lumbar facet joint injections have referred to and followed the guidelines for systematic reviews published by the Cochrane Back Review Group in 2009.[138] No systematic review authors to date

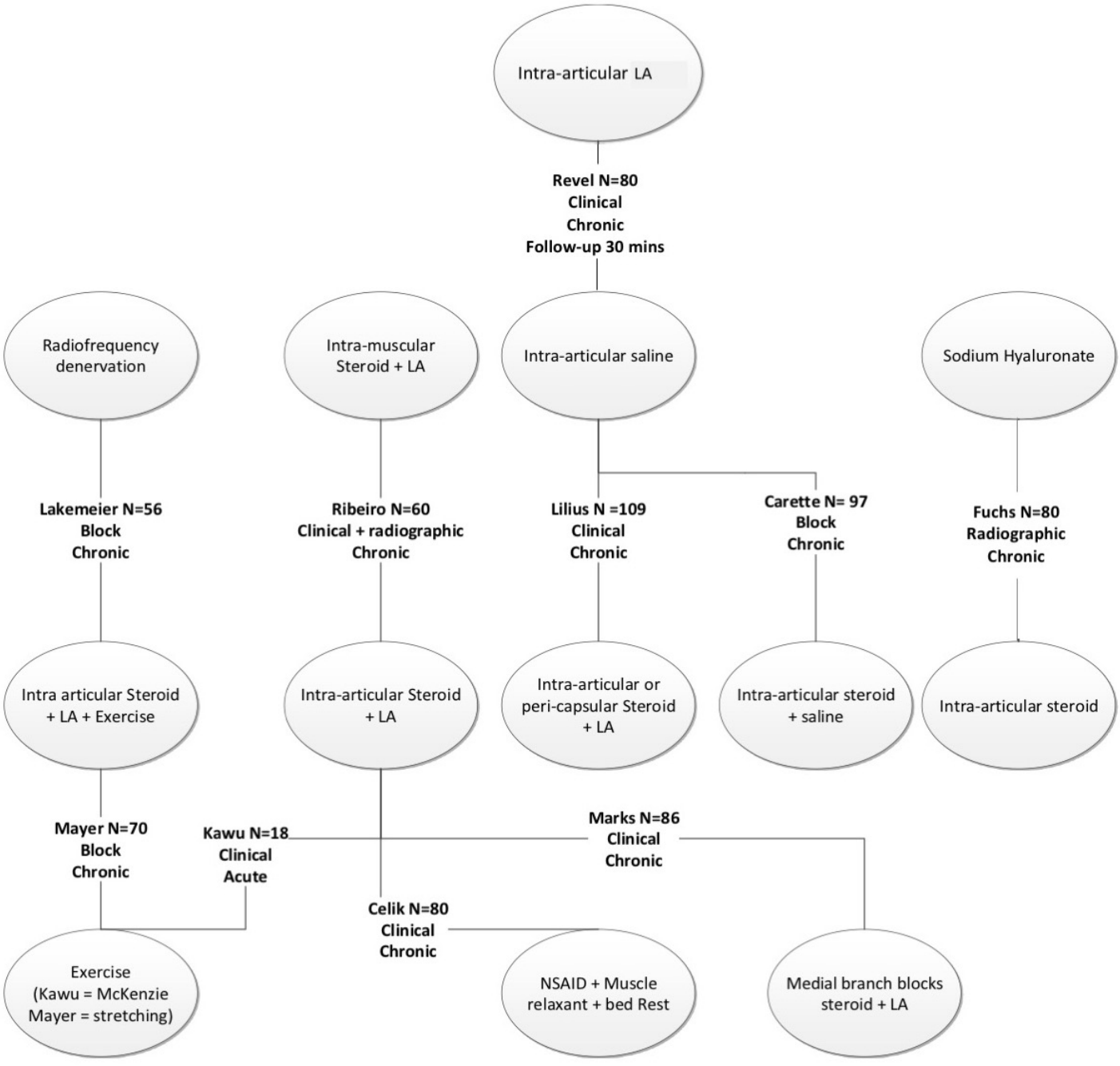
have utilised the updated guidelines, which were published in 2015 as a result of changing standards and new methodological evidence.[119] The Cochrane Handbook for Systematic Reviews of Interventions is also regularly updated,[103] reflecting the rapid pace of advancement in methodology and data extraction techniques. The last systematic review on this topic was published by Manchikanti and colleagues in 2016, who reviewed the literature until March 2015.[63] Vekaria and colleagues also published a systematic review in 2016 to assess lumbar facet joint injections, reviewing the databases from inception until April 2015.[100] Although it might be assumed that there may be new relevant randomised published controlled trials published in the intervening two years, one recently published feasibility study in the United Kingdom has outlined some of the difficulties experienced in carrying out such a study, in particular with patient recruitment.[98]

Despite a demonstrable need for a new systematic review as the current reviews are of variable methodological quality and new methodological standards has emerged since the last systematic review was published, there is arguably no current value in carrying out a new systematic review at the time of writing. The most recent high quality systematic review, which searched for trials from inception through April 2015, concluded that the included randomised controlled trials were too heterogeneous in methodology and outcome measures to carry out any meta-analyses.[100] Figure 10 illustrates the summary of designs and entry criteria of included studies, and is adapted from a figure published in this systematic review. Four randomised controlled trials identified from the other published systematic reviews have been excluded from the illustration as not meeting the Vekaria *et al.*'s criteria for inclusion; the two studies by Manchikanti and colleagues reviewed lumbar facet joint medial branch nerve blocks and not intra-articular injections,[127, 128] Yun *et al*.'s study compared different radiographic techniques,[130] and the full text for Nash's study was not available.[125] Inclusion of these studies by the systematic reviewers casts doubt on the validity of any evidence syntheses, and further demonstrates that it is not possible at present to summarise the evidence.

A future systematic review should therefore include sufficient randomised controlled trials from a homogeneous population to carry out data synthesis in

the form of a meta-analysis or meaningful data pooling. This would allow a very current research question to be addressed, as intra-articular lumbar facet joint injections are not recommended in the latest NICE guidelines for the management of LBP due to lack of evidence. It is possible that the use of new methods and the inclusion of new studies or information could change the current findings or credibility of existing systematic reviews. The research question remains highly relevant and any new information from a well-conducted review may ultimately result in a guideline change.

Figure 10. Summary of designs and entry criteria of studies published between 1966 until May 2017, adapted from Vekaria *et al*.'s systematic review.[100] Clinical = clinical assessment only, radiographic = clinical + radiological change, block = clinical + positive diagnostic block, acute = pain of less than 3 months' duration, chronic = pain over 3 months' duration. Details of the changes made to the original figure are in the preceding text.



Chapter 3: FACET feasibility study methods

A multicentre double-blind randomised controlled trial to assess the clinical- and cost-effectiveness of facet-joint injections in selected patients with non-specific low back pain: a feasibility study

Facet-joint injections for non-specific low back pain: a feasibility RCT

This randomised controlled feasibility study was accepted for publication in the NIHR Journals Library in September 2017, and published in December 2017, ahead of submission of this thesis.[99] As the lead author of the manuscript and main researcher in the study, I have attempted where possible to avoid verbatim duplication of previously published work; there however remain similarities between the text relating to the FACET feasibility study and the monograph. Any direction reproductions from the publication are acknowledged with the following statement:

Introduction to the FACET feasibility study

The rationale for carrying out a randomised controlled trial to assess the clinical- and cost-effectiveness of facet joint injections in patients with LBP has been detailed in Chapter 1. At present, there is no definitive research to support the use of targeted lumbar facet joint injections to manage chronic LBP, with current clinical guidelines not supporting their use, and inconsistent diagnostic and treatment methods. Systematic reviews of randomised controlled trials of therapeutic lumbar facet joint injections have been demonstrated in Chapter 2 to be of variable methodological quality, with conflicting conclusions.

Before undertaking a full trial to assess the clinical effectiveness and cost-effectiveness of facet joint injections compared to a sham procedure for non-specific LBP, there were questions that first need to be assessed by a feasibility study (see box 1).

Box 1. FACET feasibility study research questions

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

1. Given the multiple sites with potential to generate back pain, can patient selection criteria be optimised, using clinical and investigative diagnostic methods?

2. Can the method of injection be standardised, and an appropriate sham procedure be established?

3. Can justification for further studies to evaluate treatment methods to target and attenuate the source of chronic LBP of facet joint origin be delivered?

4. Is a sham-controlled trial design acceptable to patients and clinicians?

5. Can sufficient patients be recruited and retained?

Contributors to the study design

The FACET feasibility study design was developed by the original grant co-applicant team, with further revisions made following trial management group meetings and on the request of the funders. I wrote the detailed project description and original study protocol; any subsequent changes to the protocol are detailed further in this chapter. The statistical analysis plan, as shown in appendix 2, was written by the study statistician Professor Rod Taylor.

The members of original co-applicant team, trial management group and other contributors are listed with their contributions in the acknowledgements section of the NIHR Journals Library publication.[99]

Study design

This was a blinded parallel two-arm pilot randomised controlled trial. Participants with non-specific LBP who had a positive response to a single diagnostic medial branch nerve block were individually randomised in a 1:1 ratio to receive either the facet joint injection (active group) or a sham procedure (control group). Participants in both active and sham groups were invited to attend a combined physical and psychological (CPP) programme after their procedure.

Participants

Potential participants were screened for eligibility to enter the study based on the following inclusion and exclusion criteria (see boxes 2 and 3).

Box 2. Inclusion criteria

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

1. Patients aged 18 to 70 years attending pain clinics identified during routine clinical assessment of non-specific LBP.

   Clinical indicators for pain of facet joint origin included tenderness over the facet joints, referred leg pain above the knees, and worsening pain on extension, flexion and rotation of the lumbar spine.

2. LBP of three months' or greater duration.

3. Average pain intensity score of 4/10 or more in the seven days preceding recruitment despite NICE recommended treatment.

   NICE clinical guideline CG88 recommended providing patients with advice and information to promote self-management of their LBP, and offering one of the following treatments, taking into account patient preference: an exercise programme, a course of manual therapy, or a course of acupuncture.[29]

4. Dominantly paraspinal (not midline) tenderness at two bilateral lumbar levels.

5. At least two components of NICE-recommended best non-invasive care completed, including education and one of a physical exercise programme, acupuncture, or manual therapy.[29]

6. Patients are suitable for the facet joint injections.

Box 3. Exclusion criteria

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

1. Patient refusal to consent.
2. More than four painful lumbar facet joints.

No more than four facet joint joints were to be injected to limit the total dose of intra-articular steroids.

3. Patient has not completed at least two components of NICE-recommended best non-invasive care, including education and one of a physical exercise programme, acupuncture, or manual therapy.[29]
4. 'Red flag' signs.[a]

These are possible indicators of serious spinal pathology, and include thoracic pain, fever, unexplained weight loss, bladder or bowel dysfunction, progressive neurological deficit, and saddle anaesthesia.[139]

5. Known hypersensitivity to study medications.
6. Dominantly midline tenderness over the lumbar spine, any other dominant pain or radicular pain.
7. Any major systemic disease or mental health illness that may affect the patient's pain, disability and/or their ability to exercise and rehabilitate, as judged by the Principal Investigators.
8. Any active neoplastic disease, including primary or secondary neoplasm.

[a] These symptoms and signs were assessed by a pain clinician based on clinical history and examination.

9. Pregnant or breastfeeding patients (verbal confirmation will be obtained at screening. Prior to each interventional procedure involving x-rays, local hospital procedures will be followed to confirm that female participants are not pregnant).

10. Any evidence of previous lumbar facet joint injections, previous lumbar spinal surgery or any major trauma or infection to the lumbar spine.

11. Patients with morbid obesity (body mass index of 35 or greater).

12. Participation in another clinical trial of an investigational medicinal product or disease related intervention in the past thirty days.

13. Patients unable to commit to the six-month study duration.

14. Patients involved in legal actions or employment or benefit tribunals related to their LBP.

15. Patients with a known history of substance abuse.

Recruitment procedures

The original study protocol intended to recruit participants from pain clinics at three NHS Trusts and their associated community pain clinics. However, recruitment only took place at a single centre, at Barts Health NHS Trust, as the study was terminated early by the funder. Recruitment took place over a nine-month period, between 22nd January 2016 and 30th September 2016.

Potentially eligible participants were those with non-specific LBP who had been referred for further specialist assessment by their general practitioners (GPs). The reasons for referral included uncertain diagnosis, failure of conservative treatment, or expectation of therapeutic interventions. Patients were screened to enter the study by a pain clinician if they met the inclusion and exclusion criteria.

As described in the participant information sheet (appendix 3), 'a decision to withdraw from the study at any time will not affect the standard of care that you receive now or in the future'. Participants who withdrew from the study or who had a negative response to the diagnostic test would receive a routine pain clinic appointment to see a pain consultant.

Informed consent

Participant information sheets (appendix 3) were given to potential participants who were considered eligible to enter the study. A study researcher was available to give verbal explanation of its contents, including details of the nature of the study, the implications and constraints of the study protocol, and any known side effects and risks involved in taking part. Written informed consent, when applicable, was obtained by a medically qualified investigator on the delegation log.

Sample size calculation

The statistical analysis plan, written at the outset of the study by the study statistician Professor Rod Taylor, stated that 60 patients would be recruited, with equal allocation to active and sham groups (see appendix 2). Twenty-four full data sets per arm were expected to be completed, to give an acceptable estimate of variance of outcomes; 60 patients would give the ability to estimate the precision of an assumed 20% attrition rate with an error of ±5% at the 95% confidence level.[140]

Study interventions

Participants who were screened for eligibility and consented to enter the study received diagnostic medial branch nerve blocks. A positive response was defined as a 50% or greater pain reduction measured using a pain intensity numerical rating scale lasting over 30 minutes, assessed in the standing

position. If this was achieved, they were then randomised to active or control (sham) groups.

All the study interventions were carried out by the Principal Investigator at Barts Health NHS Trust, a Fellow of the Faculty of Pain Medicine of the Royal College of Anaesthetists in the United Kingdom. The investigator carrying out the injections was not blinded to the active or sham groups. Strict aseptic conditions were adhered to, and local theatre protocols followed with regards to admission and discharge criteria. The locally-adapted WHO Surgical Safety Checklist was used to identify the correct patient prior to starting the procedure.[141]

The diagnostic test, facet joint injections and sham procedure are detailed in boxes 4, 5 and 6 respectively.

Box 4. Diagnostic test

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

The diagnostic medial branch nerve injections were carried out at each painful lumbar level under radiological guidance. With the patient lying in the prone position on a radiolucent table, the investigator examined the patient's back to elicit paraspinal tenderness and confirmed appropriate landmarks to be injected using radiological image intensification. The C-arm of the image intensifier was obliquely rotated as required to facilitate visualisation of the target for injection. A 22G 90mm Quincke spinal needle was used to inject 0.5 ml 1% lidocaine per level, and six medial branch nerves were injected in total in each patient.

Box 5. Lumbar facet joint injections

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

In the intervention group, each participant received four facet joint injections at two bilateral lumbar levels, with 0.5 ml 0.5% bupivacaine (Marcain Polyamp Steripack 0.5%, Aspen Pharma Trading Limited, Dublin, Ireland) and 20 mg methylprednisolone (Depo-Medrone 40 mg/ml, Pfizer, Kent, UK) injected per joint. No more than four facet joints were to be injected to avoid any potential confounding effects attributable to the systematic action of exceeding 80 mg methylprednisolone. The volume of injectate did not exceed 1 ml per joint, as it would be possible to rupture the intra-articular capsule with greater volumes, spreading the local anaesthetic and steroid to other potential pain-generating structures.

Paraspinal tenderness was elicited as described previously. The skin was anaesthetised with 1% lidocaine (Lidocaine Hydrochloride BP 1% w/v, Hameln Pharmaceuticals Ltd, Gloucester, UK), and a 22G 90mm Quincke spinal needle advanced through the skin, subcutaneous tissue and paraspinal muscle towards the facet joint under x-ray guidance. Entry of the needle was confirmed by visualisation of the needle position within the joint space, and local anaesthetic and steroid was injected into the joint.

Box 6. Sham procedure

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

The control group received four injections of 0.5 ml normal saline (0.9% sodium chloride) at two bilateral lumbar levels. A low volume was chosen to avoid irritation of any structure that was part of the facet joints, including the fibrous capsule, synovial membrane, hyaline cartilage, and bone. The sham group would not receive systematic steroid administration, as it had been shown that the addition of parenteral steroid would not contribute to the pain relief achieved by targeted injections.[142]

Paraspinal tenderness was elicited as described previously. The skin was anaesthetised with 1% lidocaine, and a 22G 90mm Quincke spinal needle advanced through the skin, subcutaneous tissue and paraspinal muscle towards the peri-articular space under x-ray guidance. Placement of the needle in the peri-articular space was confirmed by visualisation of the needle position next to the joint space, and normal saline was injected at this site.

Combined physical and psychological programme

A combined physical and psychological (CPP) programme was delivered to both active and sham groups by trained physiotherapists. The CPP programme drew on the methods and evidence from the BeST trial;[83] research on CPP management of LBP has demonstrated that equally effective management can be achieved within a far shorter timeframe than 100 hours as recommended in the 2009 NICE guidance.[29]

The study physiotherapists were trained to deliver the Back Skills Training Intervention by undertaking approximately ten hours of on-line training at www.backskillstraining.co.uk (last accessed 11 November 2017), to receive a certificate of completion and a trainer manual which supported CPP programme delivery. Face-to-face meetings took place between the lead physiotherapist (Ms Stephanie Poulton) and study physiotherapists to ensure competency and standardised delivery. The CPP programme protocol is shown in box 7.

Box 7. Combined physical and psychological programme

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

Each participant attended an initial one-to-one hour-long assessment with a trained physiotherapist where information was gathered including the impact of pain on their activity, and their thoughts and beliefs regarding LBP. Individualised goals were identified with one specific to physical activity. Participants then selected and practised an individualised exercise programme.

Six weekly 1.5 hour sessions of a group-based CPP programme were scheduled for each participant. Completion of the CPP programme was defined as having completed a minimum of four out of six sessions. The session contents addressed the following:

- Understanding pain
- Pain fluctuations
- Unhelpful thoughts and feelings
- Restarting activities or hobbies
- When pain worries us
- Coping with flare ups

One session per programme was to be observed by the lead physiotherapist to assess consistency of delivery and to provide feedback and support for the physiotherapists running the course. Two research physiotherapists including the lead delivered the programme to the study participants at Barts Health NHS Trust.

Each participant received a Back Skills Training Patient Workbook which provided a summary of each week's content for their reference at home. Participants were expected to be in groups of fewer than ten; 4 to 5 groups of 4 to 5 participants per site were anticipated.

Regulatory approvals

The details of the regulatory approvals are detailed in box 8 below.

Box 8. Regulatory approvals

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

The study was conducted in compliance with the principles of the Declaration of Helsinki (1996)[143] and the principles of Good Clinical Practice[144] and in accord with all applicable regulatory requirements including but not limited to the Research Governance Framework[145] and the Medicines for Human Use (Clinical Trials) Regulations 2004,[146] as amended in 2006 and 2008, the sponsor's policies and procedures and any subsequent amendments.

The required regulatory approvals were obtained in the United Kingdom. The study received ethical approval from National Research Ethics Service (NRES) Committee London – City & East (Research Ethics Committee reference 15/LO/0500) and Clinical Trial Authorisation (CTA) from the Medicines and Healthcare products Regulatory Authority (MHRA reference 14620/0046/001-0001). The protocol was reviewed by the MHRA's clinical trials team and considered to be a Type A Clinical Trial of an Investigational Medicinal Product (CTIMP) i.e. the risks are no higher than that of standard medical care. The summary of product characteristics (SmPCs) for each investigational medical product, bupivacaine and methylprednisolone acetate, are available to view on the electronic Medicines Compendium.[147, 148] Health Research Authority (HRA) approval was obtained, and the study was given permission by the sponsor's Joint Research Management Office (JRMO) to recruit patients at Barts Health NHS Trust.

Use of ionising radiation in the study

As all the study participants would receive ionising radiation in the form of x-rays for the diagnostic injections, facet joint injections and sham procedure, imaging authorisation was sought.

The radiation dose and duration from fifteen consecutive lumbar facet joint injections were recorded by the Principal Investigator and combined by the medical physics expert with local hospital data from 810 patients undergoing similar procedures, to calculate a typical total participant dose of 0.4 mSv. The medical physics expert gave approval for the study, and requested an amendment to the participant information sheet to reflect this very low risk (see appendix 3):

'The radiation dose received has been assessed by a medical physics expert and is considered to be of very low risk, comparable to about 2 months of background radiation exposure'.

Imaging authorisation was also given by the clinical radiation expert as the participants would receive low levels of radiation exposure.

Use of methylprednisolone in the study

Participants randomised to receive intra-articular lumbar facet joint injections would receive a total of 80 mg of methylprednisolone, administered intra-articularly; this dose was chosen to avoid any potentially confounding effects due to systematic absorption (see box 5). The dose was decided by a modified Delphi survey of pain clinicians (appendix 4); the majority of those surveyed agreed that a maximum of 20 mg methylprednisolone should be injected into each of four joints.

Randomisation and blinding

Secure on-line randomisation was provided by the Peninsula Clinical Trials Unit (PenCTU), to allocate participants to either intervention or control groups in a 1:1 ratio. The randomisation system was stratified by centre with minimisation on baseline pain scores (categories).

The operator (Principal Investigator) was not blinded as the injections were intentionally given at different sites (intra-articular versus peri-articular) and the injections looked different (methylprednisolone is provided as a cloudy suspension, whereas the sham injection was clear). The study participants and the remainder of the research team, including the Chief Investigator, research nurses conducting the outcome assessments, and data analysts were blinded for the duration of the study.

The participants and the research team were unblinded at the end of the study, following completion of data analysis. In accord with sponsor guidelines, a standard operating procedure was in place in case of emergency unblinding.

Outcomes

Study participants attended for outcome questionnaire visits in research nurse-led clinics at baseline (pre-randomisation) and 6 weeks, 3 months and 6 months post-randomisation. A sample case report form (CRF) is shown in appendix 5, and the schedule of assessments is detailed in table 8.

The outcome questionnaires were chosen by members of the original co-applicant team to cover a range of pain and disability-related issues, and are in accord with the IMMPACT recommended core outcome measures for chronic pain trials.[91] Box 9 details the assessment tools used in the study.

Box 9. Assessment tools and outcome questionnaires

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

1. Pain intensity and characteristics – Brief Pain Inventory (BPI) (Short Form) Modified[149] with its 11-point numerical rating scale (NRS), and Short Form McGill Pain Questionnaire.[150] As movement could potentially influence the intervention (lumbar facet joint injections or sham procedure), all numerical rating scores were assessed in the standing position.

2. Use of co-analgesics in the previous week – participant self-report.

3. Lack of efficacy in pain relief, or, for side effects, early withdrawal from the study.

4. Expectation of benefit (asked at baseline only) – measured on a scale from 0 to 6, ranging from 'expect no improvement' to 'expect total improvement'.

5. Health-related quality of life – EuroQol-5 Dimensions five-level version EQ-5D-5L[95] and 12-Item Short Form Health Survey (SF-12).[94]

6. Functional impairment – Oswestry Low Back Pain Disability Questionnaire[93] and Pain Self Efficacy Questionnaire (PSEQ).[151]

7. Satisfaction with treatment (after treatment given) – NRS from 0 to 10 with 0 = 'extremely dissatisfied' and 10 = 'extremely satisfied'.

8. Complications and adverse events – these were the subject of enquiry at visits and following procedures, as well as being spontaneously reported at any time. They were acted on as necessary and for the patients' benefit, and were fully documented in case report forms and medical notes.

9. Co-psychological well-being – Hospital Anxiety and Depression Scale (HADS),[152] Pain Catastrophizing Scale (PCS),[153] SF-12 and BPI.

10. Healthcare utilisation and costs, and impact on productivity – Stanford Presenteeism Scale 6,[154] self-reported measures of sickness absence over the previous 3 months, and healthcare utilisation in the form of hospital visits, treatments and medications. These data were collected at each outcome visit in the case report form.

Table 8. Schedule of assessments

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

		Visit					
	Pre-screening	1	2	3	4 (6 weeks after injections ± 2 weeks)	5 (3 months after injections ± 2 weeks)	6 (6 months after injections ± 2 weeks)
Informed consent		x					
Targeted physical examination	x	x					
Inclusion/exclusion criteria fulfilled		x	x	x	x	x	x
Medical history recorded		x					
Demographic data recorded		x					
Drug history recorded		x	x	x	x	x	x
Breakthrough analgesia recorded				x	x	x	x
Adverse events			x	x	x	x	x
Outcome questionnaires		x			x	x	x
Expectation of benefit scale		x					

		Visit					
Brief Pain Inventory (Short Form)		x			x	x	x
	Pre-screening	**1**	**2**	**3**	**4**	**5**	**6**
Short-form McGill Pain Questionnaire (SF-MPQ-2)		x			x	x	x
EQ-5D-5L		x			x	x	x
12-item Short Form Health Survey (SF-12)		x			x	x	x
Oswestry Low Back Pain Disability Questionnaire		x			x	x	x
Pain Self Efficacy Questionnaire (PSEQ)		x			x	x	x
Hospital Anxiety and Depression Scale (HADS)		x			x	x	x
Pain Catastrophizing Scale (PCS)		x			x	x	x
Stanford Presenteeism Scale (SPS)		x			x	x	x
Satisfaction with treatment scale					x	x	x

Adverse events

A blinded study investigator assessed for adverse events at each study visit, and when necessary, an adverse event form was completed (see appendix 6). The adverse event management policy is shown in box 10 below.

Box 10. Adverse event management policy

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

Adverse events are defined as any untoward medical occurrence in a subject to whom a medicinal product has been administered; an adverse reaction is an untoward and unintended response in a subject to an investigational medicinal product (IMP) which is related to any dose administered to that subject. A serious adverse event or reaction results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or a congenital anomaly or birth defect. A suspected unexpected serious adverse reaction is any serious adverse event that is both suspected to be related to the IMP and unexpected.

Adverse events not already identified locally were recorded at each trial visit, and managed in accord with the sponsor's requirements. Serious adverse events were reported by the investigators within 24 hours of the research team becoming aware to the Joint Research Management Office, and causality and expectedness confirmed by the Chief Investigator, as the sponsor's medical representative.

Study management and committees

The details of the study management and committees are shown in box 11.

Box 11. Study management and committees

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

The trial management group (TMG) was responsible for the overall management of the project, and included all co-applicants and members of the study research team.

A trial steering committee (TSC) provided independent advice and support to the study, and aimed to report to the funder on study progress. It was chaired by an independent clinician with experience of pain trials.

A data monitoring committee (DMC) had access to unblinded data and made recommendations to the TSC on whether there were any ethical or safety reasons why the trial should not continue. It had independent members who were all experts in pain medicine.

Patient and public involvement

There was limited patient and public involvement in the running of the trial beyond the initial set-up stage; this will be discussed further in chapter 5.

Patient representatives, led by a Patient Liaison Group Member of the British Pain Society who was an original study co-applicant, gave advice in the early stages of study design during the trial management group meetings, advising on the acceptability of study visits and the outcome questionnaires. The

outcome questionnaires were subsequently used on volunteer patients attending the pain clinics and deemed to be acceptable. Patient representatives were invited to attend the TSC meetings.

Statistical analysis

A statistical analysis plan was prepared by the study statistician Professor Rod Taylor (see appendix 2). The baseline characteristics of both active and sham groups were to be presented descriptively with mean and standard deviations (SDs) calculated for all outcomes, and mean recruitment and attrition rates presented with 95% confidence intervals (CIs), with no inferential between- or within-group comparisons undertaken or reported. Outcome data were to be collected at baseline, then 6 weeks, 3 months and 6 months after randomisation. All statistical analyses were to be performed blinded to group allocation following the final data collection after 6 months, with no interim analyses.

Health economics analysis

A parallel health economics analysis plan was developed in collaboration with the study's health economist and statistician. A descriptive analysis of the health-related quality of life outcomes is however outside the scope of this thesis, but is published in full in the NIHR Journals Library.[99]

Summary of changes to the study protocol

Table 9 details the minor and major amendments made to the protocol over the study's duration.

Table 9. Summary of changes to the protocol

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

Amendment	Protocol version, date	Summary of changes
Minor amendment	4, 4.2.15	Update to schedule of assessment table
Substantial amendment 1	5, 2.9.15	Update to patient safety information Revised details for the trial steering committee and data monitoring committee
Substantial amendment 2	6, 7.5.16	Change of Chief Investigator and Principal Investigator at Barts Health NHS Trust Lidocaine renamed as a non-IMP Additional recruitment from spinal orthopaedic and musculoskeletal clinics

Chapter 4: Results of the FACET feasibility study

Screening and recruitment

Due to delays in study set up (the timelines and reasons for delay are presented at the end of this chapter) the funders requested that screening and recruitment take place at one centre only, at Barts Health NHS Trust; the other planned recruiting sites were Basildon and Thurrock University Hospitals and The Walton Centre in Liverpool. The recruiting sites at Barts Health NHS Trust were the pain clinics at St Bartholomew's Hospital, the spinal orthopaedic ('fracture') clinics at The Royal London Hospital, the community pain clinics at Essex Lodge GP Surgery, the pain clinics at Whipps Cross University Hospital, and the Tower Hamlets Persistent Pain Services at Mile End Hospital. The first participant was recruited from the pain clinic at St Bartholomew's Hospital on 22nd January 2016, and the study was terminated on 30th September 2016.

The Consolidated Standards for Reporting Trials (CONSORT) flow diagram (figure 11) shows that 50 out of 628 patients who were screened for eligibility to enter the study met the inclusion criteria. Sixteen participants consented to take part in the study, with five participants dropping out before receiving the diagnostic test; the eleven remaining participants all received diagnostic lumbar facet medial branch nerve blocks. Nine of these eleven participants had a positive response to the diagnostic test (82%, 95% confidence interval 48% to 98%) and were randomised to receive either lumbar facet joint injections with steroid, or a sham procedure.

Figure 11 also shows that the actual participant screening to recruitment ratio was 70:1 (628:9); the expected screening to recruitment ratio was 17:1 (1000:60) (see appendix 8 for the pre-study recruitment estimates). The median recruitment rate was 2 participants per month (see figure 10), which was lower than expected (figure 12).

Table 11 lists the reasons for screening failure, and the screening to recruitment ratio for each screening clinic at Barts Health NHS Trust is shown in table 12.

Figure 11. CONSORT flow diagram showing the flow of participants through the study

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

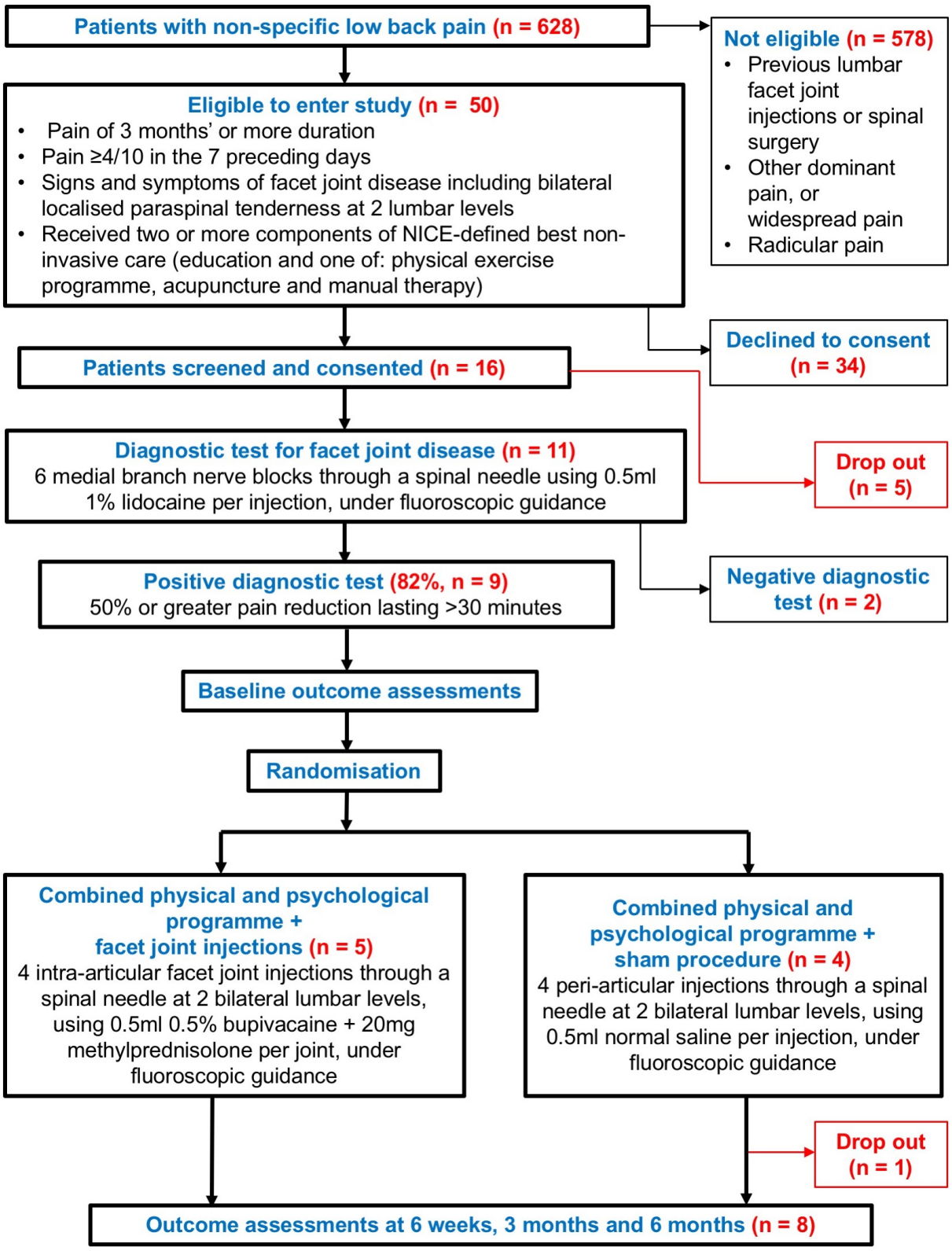


Table 10. Screening and recruitment by month

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

Outcome	Recruiting month									
	1	2	3	4	5	6	7	8	9	Total
Recruited	1	4	2	0	2	2	0	2	3	16
Screened	8	26	6	37	18	46	78	209	200	628

Figure 12. Actual and expected numbers of participants recruited at Barts Health NHS Trust for each recruitment month

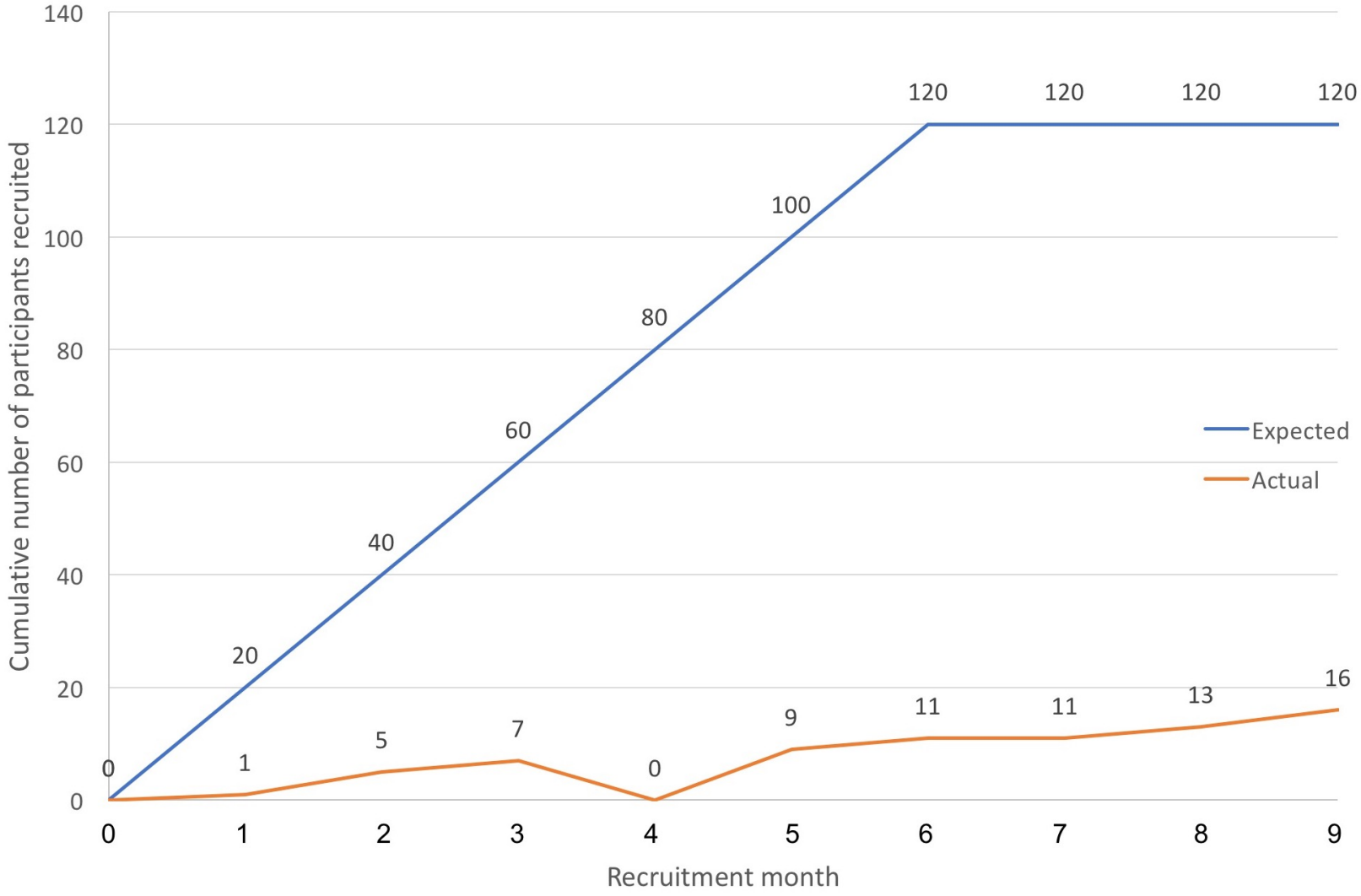


Table 11. Reasons for screening failure

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

Reasons		Number of patients
Previous lumbar facet joint injections		192
	Previous lumbar facet joint injections (163)	
	Previous lumbar facet joint injections and no previous physiotherapy (3)	
	Previous lumbar facet joint injections and radiofrequency denervation (18)	
	Previous lumbar facet joint injections or radiofrequency denervation and aged over 70 (8)	
Other dominant pain, or widespread pain		92
Radicular pain		64
Aged over 70[b]		42
	Aged over 70 (29)	
	Previous lumbar facet joint injections or radiofrequency denervation and aged over 70 (8)	
	Aged over 70 and has radicular pain (12)	
	Aged over 70 and has widespread pain (1)	
Other reasons for not meeting inclusion/exclusion criteria		36
Did not wish to take part		34
Previous major trauma to the lumbar spine		29
'Red flag' signs		29
Previous lumbar spinal surgery		25
Study team unable to contact		17
Already taking part in another study		12
Limited or no English		11
Active neoplastic disease		7
No previous physiotherapy		7

[b] Some participants were in more than one category

Morbid obesity (body mass index of 35 or greater)	7
Learning difficulties or known mental health illness	5
Known history of substance abuse	2
Aged under 18	1

Table 12. Locations of screening clinics at Barts Health NHS Trust

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

Clinic location	Numbers of patients screened for eligibility	Numbers randomised	Screened/recruited fraction %
Pain clinic, St Bartholomew's Hospital	413	7	1.69
Spinal orthopaedic ('fracture') clinic, The Royal London Hospital	180	0	0
Community pain clinic, Essex Lodge GP surgery	16	2	12.5
Pain clinic, Whipps Cross University Hospital	12	0	0
Tower Hamlets Persistent Pain Services, Mile End Hospital	7	0	0

Adherence to allocated treatment

Lumbar facet joint injections and sham procedure

The active lumbar facet joint injections and sham procedures were carried out according to the study protocol, with no study deviations or adverse events reported at the time of the procedure. The study participants did not receive additional interventional pain procedures during their time in the study.

Combined physical and psychological programme

All nine participants, regardless of their allocation group, were invited to attend a combined physical and psychological (CPP) programme; these took place after they had received their randomised procedure, between study months 12 and 20. Completion of the CPP programme was defined in the study protocol as having attended at least four out of the six sessions.

Three CPP programmes were scheduled. There were four participants in the first group, three in the second group and two in the final group.

The median number of CPP programme sessions attended by the study participants was four. There were three study deviations (less than four CPP programme sessions attended) due to illness, personal reasons relating to childcare, and unplanned overseas leave (see figure 13).

Study drop out and attrition

Five participants recruited to the study withdrew before they received their diagnostic injections, although all sixteen participants who consented to take part completed their baseline assessment questionnaires. The reasons given for drop out at this stage were not formally evaluated but included unsuitable dates for the diagnostic injections (one patient already had a date to attend for lumbar facet joint injections), and for personal or family reasons.

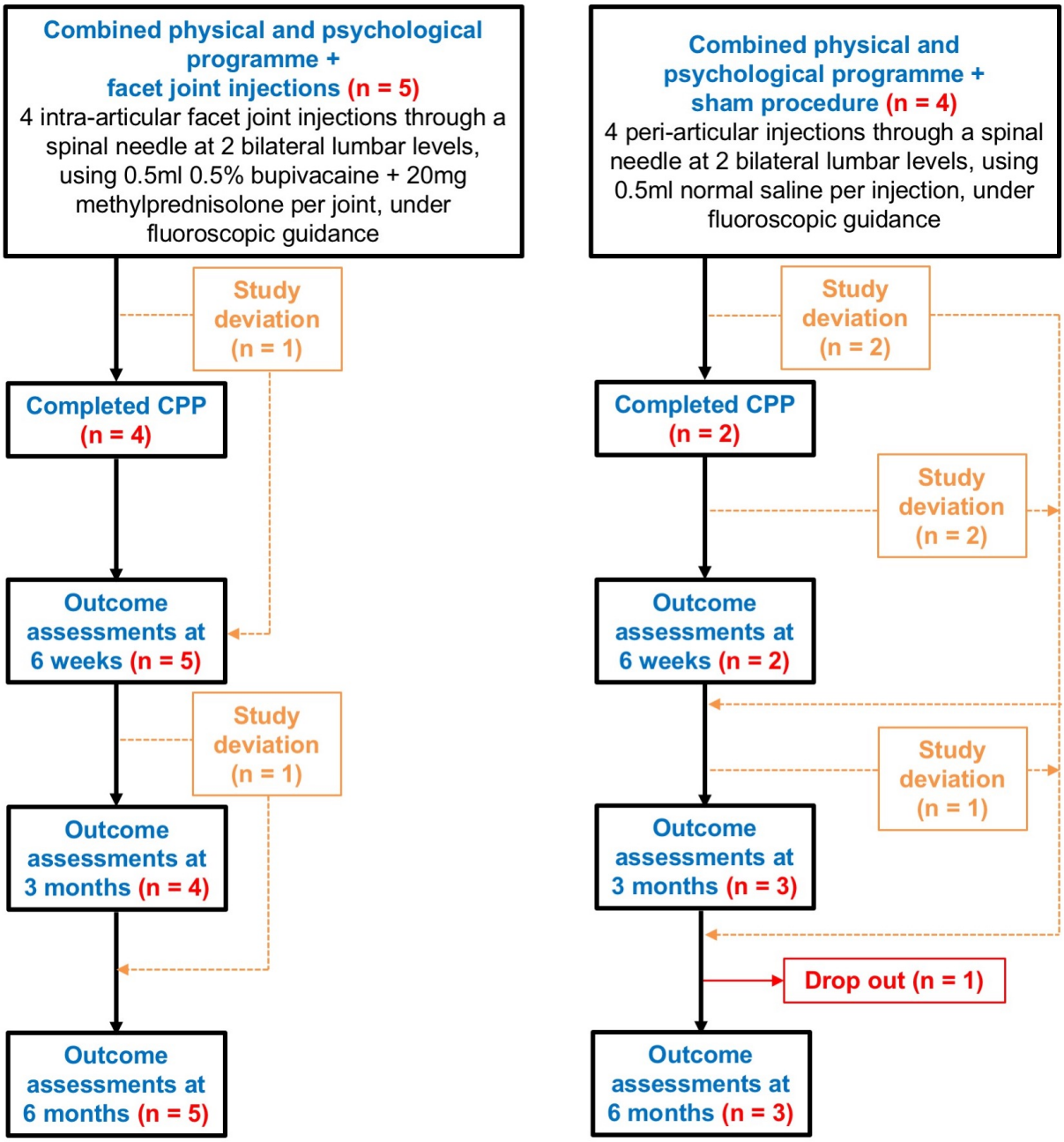
Eight participants completed the study (defined as having completed the final set of questionnaires 6 months after the randomised procedure) out of the nine participants who were randomised. The 11% attrition rate (95% confidence interval 0.2% to 48%) contrasts with expected attrition rate was 20%.

There were six study deviations; in addition to the three participants who did not complete the CPP programme, three participants did not complete all the questionnaire sets (see figure 13).

Table 20 of appendix 7 shows that there were low levels of missingness of within-questionnaire data. The study deviations and drop outs are detailed further in table 13.

Figure 13. Study deviations and study drop outs

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]



A 'study deviation' is defined as a participant who did not attend a study visit or CPP programme session, but did not drop out of the study completely.

Table 13. Data missingness, CPP programme attendance and allocation groups

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

Participant number	Questionnaires completed				Number of CPP programme sessions attended	CPP programme group	Allocation group
	Baseline	6 weeks	3 months	6 months			
1	Y	Y	Y	Y	5	1	Intervention
2	Y	N	N	Y	0	1	Sham
3	Y	Y	Y	Y	6	1	Sham
4	Y	Y	Y	Y	4	1	Intervention
5	Y	Y	Y	Y	6	2	Sham
6	Y	Y	N	Y	0	2	Intervention
7	Y	Y	Y	Y	5	2	Intervention
8	Y	Y	Y	N	0	3	Sham
9	Y	Y	Y	Y	4	3	Intervention

Baseline characteristics and outcomes

The baseline characteristics and outcomes of those who took part in the study are described in box 12 below.

Box 12. Baseline characteristics and outcomes

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

The mean age of eligible participants was 45 years, with a similar proportion of males and females. Six out of 14 participants (43%) were not working at baseline (see table 14).

Baseline patient-reported outcomes indicate a population with substantial levels of pain (mean 8.5 on a 0 to 10 visual analogue scale) that was predominantly bilateral (12/16, 75%) and which had a mean duration of 72 months (see table 14). High baseline levels of disability and mental ill health, and poor overall health-related quality of life were seen (see tables 14 and 15).

Given the small numbers randomised, not unexpectedly there was evidence of imbalance in participant characteristics and patient-reported outcomes between the two groups at baseline (see table 15).

Table 14. Participant characteristics in all eligible and randomised participants

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

	All eligible (n=16)[c]	Not randomised (n=7)	Sham group (n=4)	Intervention group (n=5)
Age (years), mean (SD)	44.8 (13.2)	44.4 (14.3)	50.5 (14.4)	40.8 (11.5)
Sex (male), n (%)	9 (56)	2 (28)	2 (50)	3 (60)
BMI (kg/m^2), mean (SD)	27.0 (5.1)	29.9 (5.1)	29.6 (4.7)	27.7 (5.6)
Baseline pain (0-10 VAS), mean (SD)	8.5 (1.5)	8.0 (1.7)	9.5 (1.0)	8.4 (1.5)
Duration of pain (months) mean (SD)	71.9 (88.7)	46.0 (53.6)	51.0 (46.3)	124.8 (135.9)
Location of pain, n (%)				
Bilateral	12 (75)	5 (71)	3 (75)	4 (80)
Unilateral	4 (25)	2 (29)	1 (25)	1 (20)
Aware of pain (years), mean (SD)	6.8 (7.6)	5.2 (4.6)	4.2 (3.9)	10.4 (11.3)
Describe health, n (%)				
Excellent	0 (0)	0 (0)	0 (0)	0 (0)

[c] Not all eligible and randomised participants contributed data

	All eligible (n=16)[c]	Not randomised (n=7)	Sham group (n=4)	Intervention group (n=5)
Very good	1 (7)	0 (0)	0 (0)	0 (0)
Good	9 (64)	3 (60)	3 (75)	1 (20)
Fair	1 (7)	1 (40)	0 (0)	3 (60)
Poor	3 (21)	1 (40)	1 (25)	1 (20)
Work status, n (%)				
Full time	7 (50)	1 (17)	2 (50)	4 (80)
Part time	1 (7)	0 (0)	1 (25)	0 (0)
Not working	4 (29)	3 (50)	0 (0)	1 (20)
Other	2 (14)	2 (3)	1 (25)	0 (0)
Illness caused stop working, n (%)				
Yes	10 (72)	1 (20)	3 (75)	3 (60)
No	4 (28)	4 (80)	1 (25)	2 (40)
Missed work days, mean (SD)	13.5 (31.1)	0 (0)	30.0 (52.0)	4.5 (3.7)
Level of activity prior to procedure, n (%)				
Hard manual	2 (29)	0 (0)	1 (33)	1 (33)
Lifting	1 (14)	1 (100)	0 (0)	0 (0)
Walking	0 (0)	0 (0)	0 (0)	0 (0)
Sedentary	4 (57)	0 (0)	2 (66)	2 (66)
Current smoker, n (%)				

	All eligible (n=16)[c]	Not randomised (n=7)	Sham group (n=4)	Intervention group (n=5)
Yes	11 (79)	2 (40)	0 (0)	1 (20)
No	3 (21)	3 (60)	4 (100)	4 (80)
Alcohol (units per week), mean (SD)	0.7 (1.1)	0.6 (1.3)	0.5 (1.0)	1.0 (1.2)
Exercise per week, n (%)				
>5 days	2 (14)	0 (0)	1 (25)	1 (20)
3-5 days	1 (7)	1 (20)	0	0
1-2 days	5 (39)	1 (20)	1 (25)	3 (60)
<1 day	6 (43)	3 (60)	2 (50)	1 (20)

Table 15. Primary and secondary outcomes at baseline

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

	All eligible (n=16)[d]	Not randomised (n=7)	Sham group (n=4)	Intervention group (n=5)
BPI (0-10), mean (SD)				
Worst pain	8.5 (1.7)	9.0 (0.9)	9.3 (1.5)	7.2 (2.2)
Least pain	6.0 (2.7)	6.2 (2.3)	6.0 (2.7)	6.0 (3.5)
Average pain	7.4 (1.5)	7.7 (1.5)	7.5 (1.9)	7.0 (1.6)
Pain now	6.5 (2.8)	5.2 (2.9)	8.0 (2.3)	6.8 (2.8)
Pain severity	7.1 (1.6)	7.0 (0.8)	7.7 (1.7)	6.8 (2.4)
General activity	7.7 (2.5)	7.7 (2.6)	9.3 (1.5)	6.6 (1.2)
Mood	6.9 (2.2)	6.7 (2.4)	7.0 (2.4)	7.0 (4.8)
Walking ability	6.3 (2.8)	6.2 (2.3)	5.5 (2.0)	7.0 (2.7)
Normal work	8.1 (2.2)	8.5 (2.1)	8.5 (1.7)	7.2 (2.9)
Relations	6.2 (2.5)	5.3 (3.3)	6.5 (1.9)	7.0 (4.8)
Sleep	7.1 (3.0)	5.8 (3.5)	8.8 (1.9)	7.4 (3.0)
Enjoyment	7.4 (3.0)	6.8 (3.9)	8.3 (1.7)	7.4 (3.0)
Interference	7.1 (3.9)	6.7 (4.7)	7.7 (1.8)	7.1 (2.4)

[d] For some outcomes only 14 participants contributed data

	All eligible (n=16)[d]	Not randomised (n=7)	Sham group (n=4)	Intervention group (n=5)
McGill Pain Questionnaire, mean (SD)				
Continuous pain	5.2 (2.0)	5.6 (0.9)	4.5 (3.0)	5.3 (2.2)
Intermittent pain	4.4 (2.5)	4.7 (2.4)	4.2 (2.6)	4.3 (3.1)
Neuropathic pain	2.7 (1.9)	2.7 (2.2)	2.1 (1.8)	3.2 (1.7)
Affective descriptors	4.0 (2.6)	3.9 (2.8)	2.0 (1.5)	5.6 (2.4)
Total	4.1 (1.7)	4.2 (1.5)	3.3 (2.0)	4.5 (2.0)
Oswestry Disability Index, mean (SD)				
Total	49.2 (17.6)	55.8 (19.4)	48.8 (19.9)	43.0 (15.0)
Pain Self Efficacy Questionnaire, mean (SD) Total	21.3 (12.8)	16.5 (15.8)	27.0 (7.7)	22.6 (12.2)
SF-12, mean (SD)				
PCS	33.5 (5.8)	34.5 (5.8)	32.7 (6.0)	33.1 (6.7)
MCS	35.7 (11.2)	34.7 (14.7)	43.4 (10.0)	30.4 (4.6)
Hospital Anxiety and Depression Score, mean (SD)				
Anxiety	10.1 (4.0)	10.3 (5.2)	7.5 (3.4)	12.0 (1.2)
Depression	9.7 (4.1)	11.0 (4.8)	6.8 (3.9)	10.4 (3.4)
Pain Catastrophizing Scale, mean (SD)				
Rumination	12.5 (3.9)	11.7 (4.9)	11.5 (4.0)	14.2 (2.5)

	All eligible (n=16)[d]	Not randomised (n=7)	Sham group (n=4)	Intervention group (n=5)
Magnification	7.1 (3.3)	6.8 (3.3)	6.3 (4.3)	8.0 (3.2)
Helplessness	15.7 (4.4)	16.3 (4.8)	11.7 (4.4)	18.0 (4.8)
Total	35.2 (11.1)	34.8 (11.7)	29.5 (12.3)	40.2 (9.0)
EQ-5D-5L index, mean (SD)	0.41 (0.30)	0.43 (0.29)	0.40 (0.21)	0.39 (0.35)
Expectation of benefit, mean (SD)	3.3 (1.7)	2.7 (2.4)	3.5 (0.6)	3.8 (1.1)

Primary and secondary outcomes at follow-up

The primary and secondary results at 6 weeks' and 3 and 6 months' follow-up are presented descriptively, according to the statistical analysis plan (see table 16).

Table 16. Summary of descriptive outcomes at all follow-up points. Primary and secondary outcomes at follow-up

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

Outcome	Follow-up time point, mean score (SD)					
	6 weeks		3 months		6 months	
	Sham group (n=2)	Intervention group (n=5)	Sham group (n=3)	Intervention group (n=4)	Sham group (n=3)	Intervention group (n=5)
BPI (0-10), mean (SD)						
Worst pain	5.0 (2.8)	7.8 (1.9)	7.3 (3.0)	7.8 (1.7)	6.3 (4.7)	6.0 (3.5)
Least pain	4.0 (1.4)	5.2 (2.5)	7.0 (3.6)	5.3 (2.2)	5.3 (4.5)	5.0 (2.8)
Average pain	4.5 (2.1)	6.2 (2.5)	6.0 (2.6)	6.3 (2.5)	5.3 (4.5)	5.6 (2.6)
Pain now	5.0 (2.8)	6.6 (2.1)	6.3 (3.0)	5.8 (2.1)	6.0 (4.6)	5.2 (3.7)
Pain severity	4.6 (2.3)	6.5 (2.1)	6.7 (3.0)	6.3 (2.1)	5.8 (4.5)	5.5 (3.1)
General activity	5.0 (4.2)	6.2 (2.4)	6.7 (2.3)	7.3 (1.9)	6.0 (5.3)	5.6 (3.6)
Mood	4.5 (2.1)	7.2 (1.9)	7.0 (3.6)	7.8 (2.1)	5.3 (5.0)	5.6 (3.6)
Walking ability	4.0 (1.4)	7.2 (2.6)	5.3 (1.5)	6.0 (2.9)	4.3 (4.9)	5.0 (4.6)
Normal work	5.5 (0.7)	7.2 (2.6)	6.0 (2.0)	6.8 (2.8)	5.0 (5.0)	6.0 (4.7)

Outcome	Follow-up time point, mean score (SD)					
	6 weeks		3 months		6 months	
	Sham group (n=2)	Intervention group (n=5)	Sham group (n=3)	Intervention group (n=4)	Sham group (n=3)	Intervention group (n=5)
Relations	3.5 (2.1)	6.2 (3.4)	5.7 (4.0)	7.5 (1.9)	4.0 (5.3)	5.2 (3.2)
Sleep	6.5 (4.9)	8.0 (1.9)	7.0 (2.6)	6.3 (2.9)	4.3 (5.1)	6.0 (4.7)
Enjoyment	4.5 (2.1)	7.6 (2.3)	7.7 (2.5)	7.0 (2.2)	4.7 (4.7)	6.2 (3.3)
Interference	4.8 (2.1)	7.1 (1.9)	6.5 (2.4)	6.9 (2.2)	4.8 (4.9)	5.7 (3.8)
McGill Pain Questionnaire, mean (SD)						
Continuous pain	3.8 (3.2)	4.9 (3.1)	6.3 (3.4)	3.9 (1.4)	4.1 (3.7)	3.3 (2.6)
Intermittent pain	4.4 (3.7)	3.7 (2.5)	4.9 (3.0)	3.7 (3.5)	3.5 (2.9	3.6 (3.8)
Neuropathic pain	1.7 (1.8)	4.0 (3.2)	2.5 (1.5)	2.0 (0.9)	3.6 (3.4)	3.0 (2.9)
Affective descriptors	4.4 (4.8)	4.6 (3.0)	5.6 (4.0)	5.4 (1.2)	2.5 (2.5)	3.7 (2.8)
Total	3.5 (3.3)	4.2 (2.3)	4.8 (2.6)	3.6 (1.5)	3.5 (2.9)	3.4 (2.8)
Oswestry Disability Index, mean (SD)						
Total	36.0 (17.0)	48.4 (20.2)	56.0 (14.4)	39.0 (9.9)	42.6 (34.0)	39.9 (26.0)

Outcome	Follow-up time point, mean score (SD)					
	6 weeks		3 months		6 months	
	Sham group (n=2)	Intervention group (n=5)	Sham group (n=3)	Intervention group (n=4)	Sham group (n=3)	Intervention group (n=5)
Pain Self Efficacy Questionnaire, mean (SD) Total	33.5 (10.6)	21.2 (15.3)	27.7 (9.6)	31.8 (14.1)	28.3 (21.7)	33.2 (19.4)
SF-12, mean (SD) PCS MCS	38.8 (10.3) 43.6 (15.4)	33.7 (8.6) 31.3 (7.9)	38.5 (6.8) 35.7 (7.8)	40.8 (11.0) 37.8 (2.6)	34.4 (12.5) 47.2 (22.1)	39.5 (13.7) 38.1 (13.5)
Hospital Anxiety and Depression Score, mean (SD) Anxiety Depression	7.0 (1.4) 4.0 (4.3)	12.8 (4.4) 10.8 (6.7)	8.3 (3.8) 8.0 (3.5)	11.5 (4.6) 9.5 (5.5)	6.7 (5.7) 7.7 (8.1)	10.0 (3.9) 8.4 (7.1)

Outcome	Follow-up time point, mean score (SD)					
	6 weeks		3 months		6 months	
	Sham group (n=2)	Intervention group (n=5)	Sham group (n=3)	Intervention group (n=4)	Sham group (n=3)	Intervention group (n=5)
Pain Catastrophizing Scale, mean (SD)						
Rumination	11.0 (1.4)	12.4 (4.9)	15.0 (1.0)	11.8 (4.8)	15.8 (3.8)	14.4 (5.5)
Magnification	8.0 (1.4)	6.6 (2.9)	10.3 (0.6)	5.0 (3.5)	19.5 (3.5)	13.8 (5.9)
Helplessness	14.0 (2.8)	15.0 (7.0)	13.7 (6.5)	15.0 (8.9)	16.7 (6.1)	15.5 (9.0)
Total	33.0 (5.6)	34.0 (14.0)	19.0 (6.6)	32.7 (17.2)	16.7 (7.6)	16.0 (7.4)
EQ-5D-5L index, mean (SD)	0.67 (0.30)	0.43 (0.33)	0.42 (0.10)	0.62 (0.28)	0.60 (0.50)	0.51 (0.41)
Satisfaction, mean (SD)	6.3 (3.8)	6.6 (0.9)	7.3 (1.2)	7.5 (0.6)	9.7 (0.6)	6.0 (2.1)

Adverse events

Three study participants reported adverse events. These are detailed further in table 17.

Table 17. Summary of adverse events

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

Participant number	Description of adverse event	Relationship to IMP, as judged by the Principal Investigator	Seriousness of adverse event, as judged by the Principal Investigator	Randomisation group
1	Flare-up of LBP after randomised procedure	Expected reaction, related to IMP	Not serious	Sham
4	Flare-up of LBP 5 months after randomised procedure	Expected reaction, related to IMP	Not serious	Intervention
7	Urinary incontinence	Unexpected reaction, not related to IMP	Serious adverse event (required overnight stay in hospital)	Intervention
	Swelling at site of injections	Expected reaction, related to the procedure but not to the IMP	Serious adverse reaction (required overnight stay in hospital)	
	Flare-up of LBP after randomised procedure	Expected reaction, related to IMP	Not serious	

	Flare-up of LBP 5 months after randomised procedure	Expected reaction, related to IMP	Not serious	

Blinding to treatment allocation

Prior to being unblinded at the end of the study, the eight participants and blinded outcome assessor were asked to guess which allocation group they thought the participant had belonged to. One out of eight participants guessed correctly, whereas the outcome assessor guessed correctly four out of nine times. The implications of this will be discussed in the following chapter.

Study timelines

The study timelines and Gantt chart are shown in figures 14 and 15 respectively. The start date was delayed by 18 months (546 days) from the original contract start date, with delays in obtaining NHS permission to recruit. The funders granted a no-cost negotiated one-month extension period which allowed for timely collection of follow-up data and delivery of the final report.

Figure 14. Study timelines and milestones

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

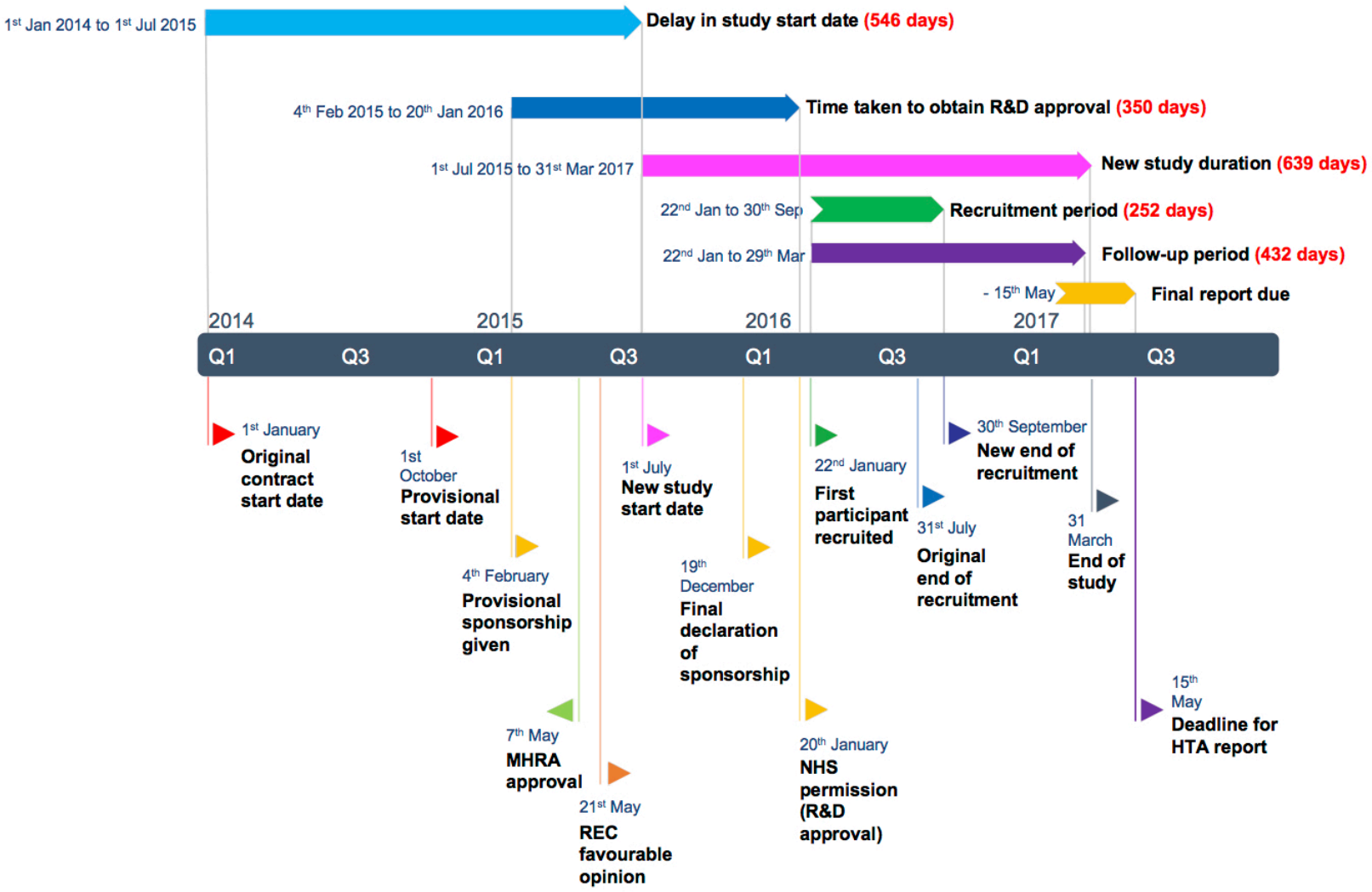
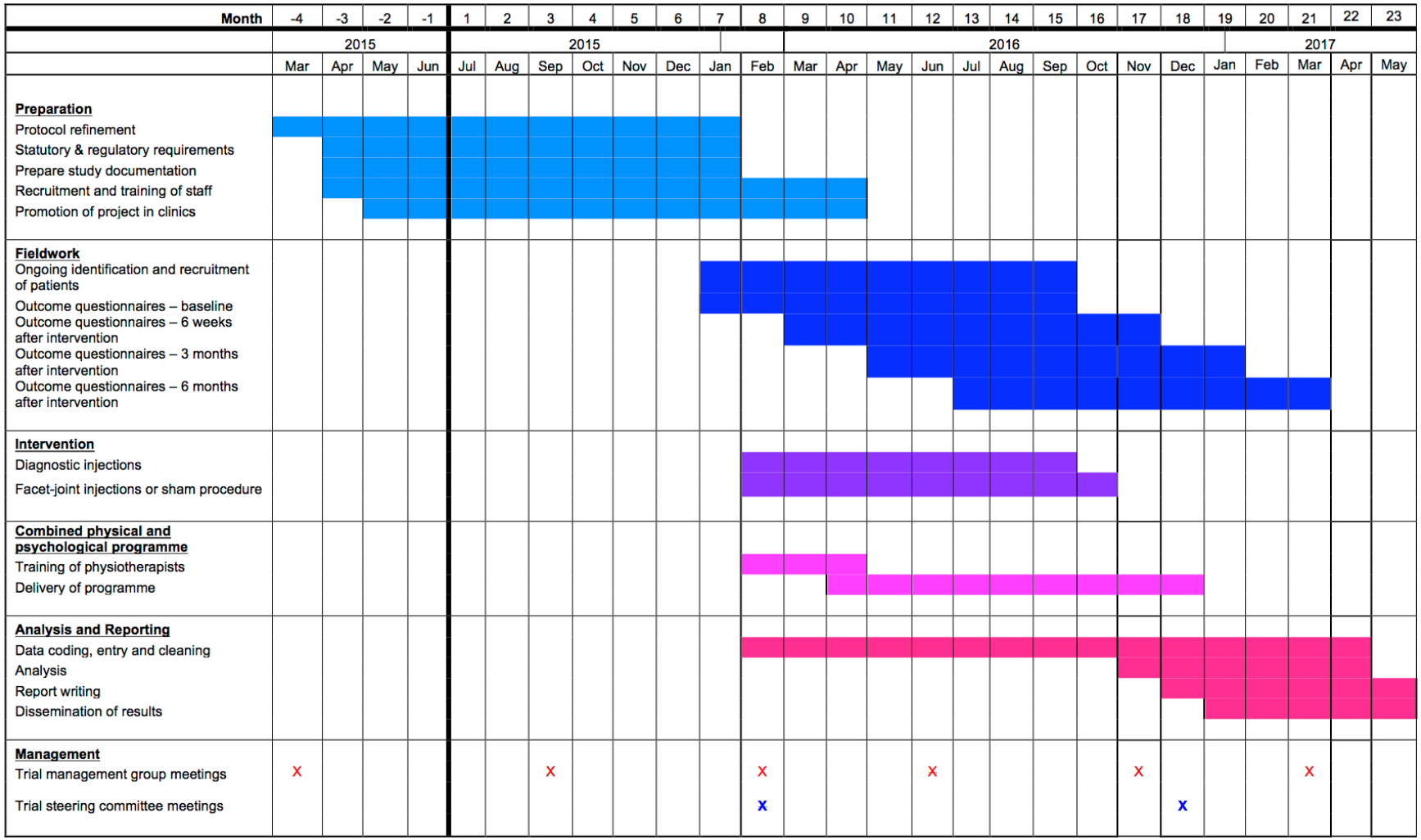


Figure 15. Study GANTT chart

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]



Chapter 5: Discussion

Summary of findings

Critical appraisal of systematic reviews

A literature search to identify systematic reviews and meta-analyses of randomised controlled trials of intra-articular lumbar facet joint injections for chronic LBP management retrieved a total of 14 randomised controlled trials across 11 systematic reviews, and no meta-analyses. None of the review authors were able to pool the data due to the level of clinical heterogeneity detected across the randomised controlled trials which compared different injection procedures, substances and comparators, from a heterogeneous population.

No clear conclusions can be drawn from the existing systematic reviews which were themselves of variable methodological quality, and the evidence to support the use therapeutic lumbar facet joint injections for the management of chronic LBP remains lacking despite some limited trial evidence. Vekaria and colleagues, who carried out a well-designed systematic review of randomised controlled trials published from inception until April 2015, summarised the current evidence base as follows:

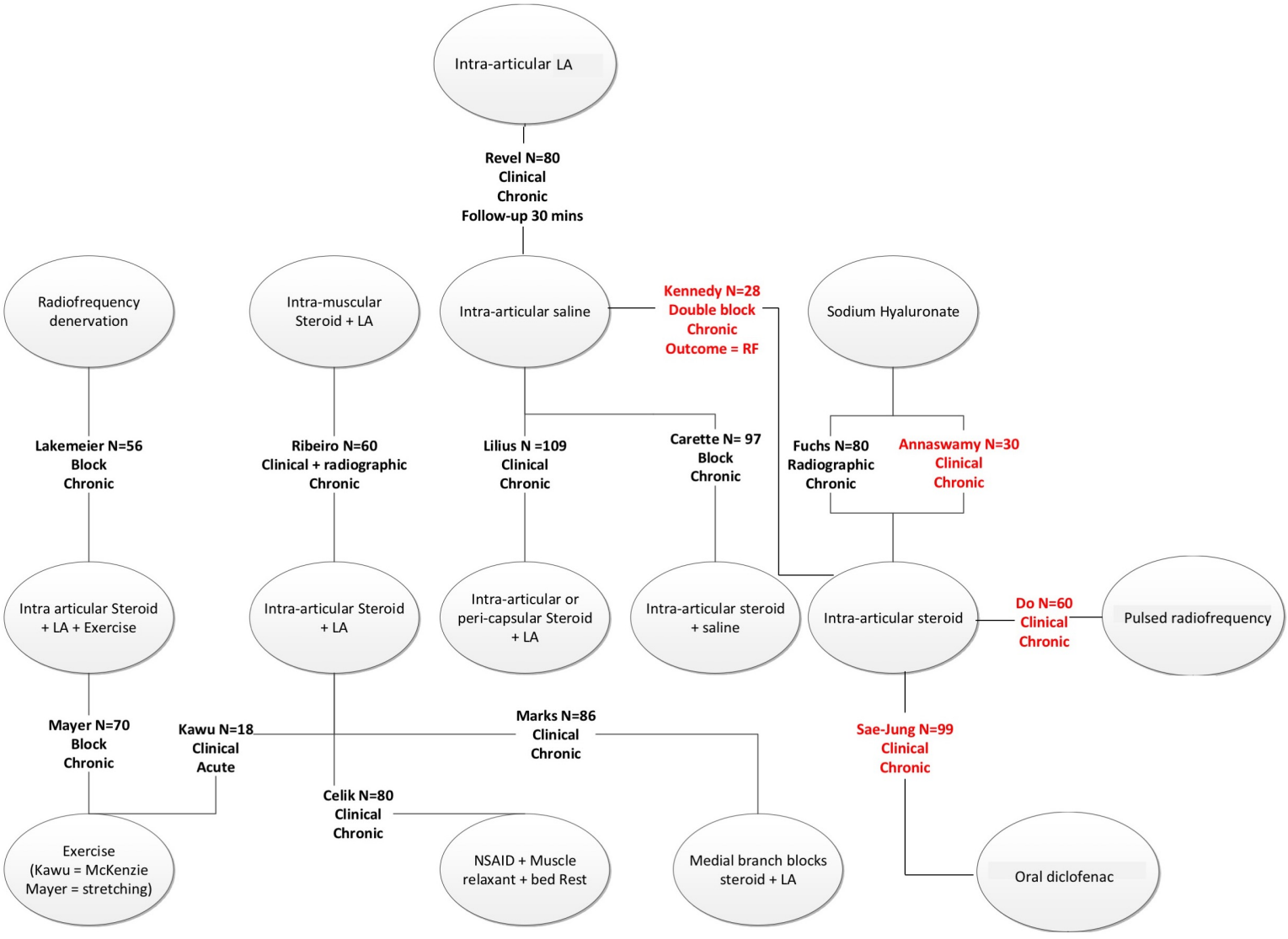
'The studies found here were clinically diverse and precluded any meta-analysis. A number of methodological issues were identified. The positive results, whilst interpreted with caution, do suggest that there is a need for further high-quality work in this area.'[100]

The literature search period for the critical appraisal of systematic reviews in chapter 2 was between 1966 until May 2017; when this search was repeated twelve months later in May 2018, a further 4 randomised controlled trials were

identified[155-158]. It can however be seen that even these latest trials are diverse and any attempts to pool their results will not meaningful (see figure 16).

It is not possible at present to summarise the available evidence for lumbar facet joint injections in chronic LBP management. The randomised controlled trials have recruited from a heterogeneous population, with no standardised inclusion and exclusion criteria, and there remains no agreement between the researchers on how to accurately diagnose pain of lumbar facet joint origin. There remain significant challenges in the interpretation of some systematic review findings, due to the inclusion of poor quality studies and weak methodology.

Figure 16. Summary of designs and entry criteria of studies published between 1966 until May 2018, adapted from Vekaria *et al*.'s systematic review.[100] Clinical = clinical assessment only, radiographic = clinical + radiological change, block = clinical + positive diagnostic block, acute = pain of less than 3 months' duration, chronic = pain over 3 months' duration. The studies in red were published between May 2017 and May 2018.



FACET feasibility study

The FACET feasibility study's overarching aim was to assess the feasibility of conducting a definitive study evaluating the clinical- and cost-effectiveness of facet joint injections compared with a sham procedure, in patients with non-specific LBP of more than three months' duration. The parallel health economics analysis is outside the scope of thesis but is presented separately in the NIHR Journals Library's publication 'Facet-joint injections for non-specific low back pain: a feasibility RCT'.[99]

No definitive conclusions can be drawn on the clinical effectiveness or cost effectiveness of intra-articular lumbar facet joint injections for the management of non-specific LBP, due to the constraints of this being a single centre study with small patient numbers; the feasibility recruitment target of sixty randomised patients at three NHS Trusts was not met, and only nine participants were randomised at a single recruiting centre. The attrition rate was low, although the small sample size precludes any definitive conclusions on patient retention. No significant adverse events, as judged by the clinical research team, were reported as a consequence of the interventional procedures.

The feasibility study showed good adherence to the statistical analysis plan, and many of the clinical outcomes were successfully collected over the duration of the study. The sample size however meant that it was not possible to interpret the numerical differences in outcomes observed between the two treatment arms.

Many of the feasibility objectives, listed in box 13, were met. The detailed objectives will be discussed further in this section.

Box 13. Feasibility objectives achieved by the FACET feasibility study

Adapted from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

1. Selection of patients into the study using a joint clinical and diagnostic approach.

2. Successful standardisation of the methods of facet joint injection and the sham procedure, using a modified Delphi method to generate consensus amongst interventional pain specialists in the United Kingdom.

3. Ability to carry out the sham procedure (peri-articular injections with saline) in participants randomised to the control group.

4. The sham-control study design was accepted by the clinicians involved in the study, and was also deemed acceptable by patients.

5. Participants were retained over the 6-month follow-up period.

To assess the eligibility criteria, recruitment and retention of patients in the two treatment arms

The considerable delays in obtaining permission to recruit participants to the study (see figure 14) resulted in a funder-led decision to terminate the study early. Recruitment therefore only took place at a single centre, as there was insufficient time available to open the other two sites. Some of the reasons for delay will be discussed further in this chapter.

One striking finding of the feasibility study was the high screening to recruitment ratio of approximately 70:1; 628 participants were screened to randomise nine participants. It can be seen in appendix 8 that the pre-study screening to recruitment ratio estimate was 17:1 (1000:60). A lack of formal process evaluation meant that this discrepancy was discussed instead at each trial management group meeting, when the screening logs were also reviewed. It was noted that patients who were aged over 70 who would otherwise have been suitable were excluded from the study; table 11 shows that out 628 patients screened, 42 were aged over 70 and 29 met the entry criteria. Although a decision was made not to amend the existing study protocol, a future trial may wish to broaden the entry criteria by increasing or removing the upper age limit. The screening to recruitment ratio derived from this feasibility study has some precision in the context of the hospital pain and spinal orthopaedic clinics at Barts Health NHS Trust and is applicable to this patient sub-group, but may not apply to other centres or to primary care.

The expected level of attrition was 20%, as defined in the statistical analysis plan and protocol; five participants dropped out of the study after giving consent but prior to receiving the diagnostic test, and one randomised participant did not complete the study i.e. did not complete the final set of questionnaires six months post-randomisation. Although this feasibility study shows an apparently high level of participant retention, the sample size is too imprecise to calculate the attrition rate with any degree of precision (11% attrition rate, 95% confidence interval 0.2% to 48%).

To assess the feasibility and acceptability of the two treatment arms from the point of view of patients and their pain teams

A modified Delphi survey of approximately 250 pain specialists in the United Kingdom was undertaken to achieve a consensus on the choice and maximum dose of steroid for the facet joint injections, the volume to inject into each joint, and on the technique for the sham procedure (see appendix 4); the facet joint injections and sham procedure can therefore be considered acceptable to pain clinicians as 42 took part in the survey. The pain and spinal orthopaedic teams and research physiotherapists at Barts Health NHS Trust all screened and recruited participants to the study, indicating its feasibility and acceptability to clinicians.

The CONSORT flow diagram, shown in figure 7, illustrates that 34 patients referred to the pain clinics by their GPs with LBP met the eligibility criteria but declined to take part in the study. Although a formal process evaluation was not undertaken, the two treatment arms were not cited as a reason for not wishing to take part.

To assess the feasibility of the proposed definitive study design

Many aspects of the proposed definitive study design were shown to be feasible within the constraints of this study. The research team received training to use the web-based randomisation system, with no reports of technical difficulties or unintentional unblinding. Some fidelity of blinding was demonstrated as nearly 50% of the allocation groups were correctly guessed by the blinded outcome assessor, and only one out of eight participants who completed the study correctly guessed their allocation group.

Appropriate active intra-articular lumbar facet joint injections and sham peri-articular saline injection techniques were developed using a consensus technique, and no protocol deviations were reported in their delivery.

The outcomes proposed for the main trial were collected in the majority of participants; however, eleven participants returned incomplete questionnaire

sets, as shown in table 20 of appendix 7. The level of missingness ranged from individual questions being omitted or spoiled (illegible), to missed questionnaire visits. Feasibility was demonstrated in study data collection, as baseline data was collected in all participants who consented to take part in the study, and in most participants at six weeks, three months and six months' post-randomisation. High quality data entry was ensured by the use of manual double data entry onto the electronic database by two independent research team members.[159]

The feasibility study protocol and detailed project description was written in 2012; the 2009 NICE guidelines for the early management of persistent non-specific LBP (NICE CG88) had recommended around 100 hours of a CPP programme over a maximum of eight weeks to those who had already received at least one less intensive treatment such as an exercise programme, manual therapy or acupuncture, and with 'high disability and/or significant psychological distress'.[29] It was however decided by the trial management group to draw on the evidence from the BeST trial as a 100-hour CPP programme was not usual NHS practice at the time of the commissioned call; this would allow for the CPP programme to be effectively delivered to groups of six to ten participants within a far shorter timeframe.[83]

The NICE guidelines for LBP management was updated in November 2016, two months after the feasibility study's recruitment period had ended.[25] This guidance similarly followed the evidence from the BeST trial and did not prescribe the length and duration of the CPP programme; a programme was to be considered in those with LBP or sciatica when there were 'significant psychosocial obstacles to recovery', and when previous treatments were ineffective. The CPP programme delivered in the FACET feasibility study can therefore be considered to be well aligned with this current guidance.

Delivery of the CPP programme proved to be feasible at the single recruiting centre; all the study physiotherapists across the three planned recruiting sites were trained by the lead physiotherapist (Ms Stephanie Poulton) to deliver the CPP programme, with no protocol deviations. Three programmes were delivered at Barts Health NHS Trust although fewer participants attended per

group than expected, with between one and three participants per group. The protocol defined successful completion of the CPP programme as having attended at least four out of the six sessions; six out nine randomised participants completed the CPP programme. The reasons given for incomplete or non-attendance included illness, undisclosed personal reasons, and travel abroad.

To estimate outcome standard deviation to inform the power calculation for a definitive study

Good adherence to the statistical analysis plan was demonstrated, despite the small final sample size. As shown in chapter 4, the participant characteristics for all study participants were described, with mean and standard deviation for the primary and secondary outcomes reported at baseline and follow-ups.

It is however not advisable to use these outcome standard deviations to inform the power calculation for a definitive study. The study statistician (Professor Rod Taylor) used a calculation based on a simulation study by Teare and colleagues, which recommended at least 35 participants per group to estimate a standard deviation for a continuous outcome in an external pilot or feasibility study; the larger the sample size, the more precise the estimate.[160]

To finalise the protocol design, statistical plan, number of centres required and study duration of the definitive study

It was not possible to finalise the protocol design for the definitive trial on the basis of this feasibility study, as the recruitment target was not reached, and participants were recruited from a single centre only. However, important lessons have been learned here which should be considered by future researchers when planning a trial of injection therapy for chronic LBP management; the implications of the FACET feasibility study for future research will be discussed later in this chapter.

Issues encountered and how they were resolved

The following section outlines the regulatory and staffing issues encountered, and the challenges experienced with recruitment including with clinician and patient participation and with the study population itself. The importance of trial management and trial mentorship will also be discussed.

Regulatory issues

Figure 14 illustrates the delays experienced by the research team in particular at a local level, in part due to the length of time taken for any issues to be addressed. System errors caused delays in gaining NIHR portfolio adoption and NHS permission to recruit. There were additional delays in obtaining signed contracts between the proposed collaborating centres.

The processes required for gaining research governance approval to carry out a clinical trial can lead to significant delays in a study's schedule. Thompson and France presented a narrative case study where unexplained delays in obtaining Research Management and Governance approval in England but not Scotland, for a multicentre observational study, were caused in part by the research governance teams offering contradictory advice, lack of familiarity with the new systems and processes, and by a lack of clear training and guidance.[161] Consequently, the researchers had to revise and scale down their objectives, which they were unable to fully deliver within the funding timescale. Difficulties were also experienced in recruiting from general practices in England, as the Primary Care Research Networks would not allow the practices to be used as Patient Identification Centres until governance approvals had been granted.

Kearney and colleagues investigated and analysed the delays in opening research sites for multicentre clinical trials in the United Kingdom, which the group identified as a high priority and potential barrier in improving the country's research profile in a competitive market.[162] The group noted that the United Kingdom may not at present be an attractive location to conduct clinical trials, due to these perceived barriers and delays, although the delays may be reduced by government-initiated targets and the National Institute for Health Research Clinical Research Network initiatives. This prospective study found that the median time to open the participating sites from the date of the ethics

letter confirming the sites' participation in the trial was 10.5 months (interquartile range 7.3 to 15.2), which increased to 14.5 months (interquartile range 11.4 to 16) for the first 17 sites. The authors noted that research applications were not being reviewed during the period of NHS restructuring and the formation of Clinical Commissioning Groups which came into effect in April 2013.

The inconsistencies found across the NHS in gaining research permission, with considerable duplication in the application processes and multiple requests for information led to the development of a new process to streamline the research regulatory pathway, with Health Research Authority (HRA) Approval replacing the previous NHS Permissions from 2014 with a full roll out of all NHS studies in England from the end of March 2016. Although single centre studies (where the sponsor is also the recruiting site) were initially excluded during the early roll out phase, HRA Approval is now required of all trials.

Many of the regulatory issues experienced were out of the research team's control; the study's timescale coincided with a time of change within research governance, and lack of guidance and clear dissemination of information from the local research governance team meant that the clinical research team were unaware of the changes in the permissions process, further delaying the start of the study whilst waiting to obtain HRA Approval.

Staffing issues

Key members of the original co-applicant team withdrew from the study as the projected study period was delayed during the regulatory approval processes. Both the Chief Investigator (Professor Richard Langford) and lead physiotherapist (Professor Paul Watson) retired from clinical practice, a new trial co-ordinator was appointed, and other key members including the lead psychologist (Professor Amanda Williams) had conflicting interests and priorities.

Staffing issues were noted also within the local research governance team; this included several changes of trial pharmacist and a change of trial monitor immediately prior to gaining NHS permission to recruit. The turnover rate of

research staff caused duplication of work due to inadequate handover. The new trial monitor requested further substantial amendments to the trial protocol which delayed the start of study recruitment.

Recruitment challenges

A significant proportion of patients referred by their GP to the pain clinics with persistent LBP did not meet the eligibility criteria, for the reasons detailed in table 11. The low recruitment rate led to a request from the funders to appoint a trial mentor who was an experienced triallist; the trial mentor led a recruitment drive within the last two months of the recruitment phase and the resulting increase in numbers of patients screened is illustrated in figure 17. The strategies employed to improve recruitment included minor protocol amendments within the constraints of the existing study entry criteria to screen and recruit from community pain clinics, physiotherapy-based musculoskeletal clinics and spinal orthopaedic clinics, and the appointment of additional research assistants to assist with the screening process. The trial mentor also negotiated a no-cost recruitment extension period which was granted by the funder.

It may be possible to avoid some of these recruitment challenges by the early addition of a recruitment co-ordinator to the core study team, to closely monitor the recruitment rate at each site, and to implement *a priori* contingency plans with the sites' Principal Investigators should the recruitment rate fall below the predicted rate. Some of the strategies successfully implemented by the trial mentor for the FACET feasibility study could be used by future researchers to improve the recruitment rate.

Recruitment problems have been identified as one of the most difficult challenges in conducting a clinical trial; Dal-Ré and colleagues have called for greater transparency in the disclosure of recruitment performance of each site investigator, which could potentially highlight differences in standards of care at each site.[163] This group noted that many clinical trials, both publicly-funded and industry-sponsored, do not achieve the expected sample size before

termination, and are unable to test the proposed hypothesis. However, improved transparency will not necessarily improve recruitment.

The Strategies for Trial Enrolment and Participation Study (STEPS) was a three-part study aimed at identifying factors associated with good or poor recruitment in multicentre trials.[164] Successful trial recruitment was observed more commonly in trials with a dedicated trial manager, in cancer or drug trials, and in trials with interventions that were exclusive to that particular study. McDonald and colleagues (the STEPS group) reviewed 114 trials funded in the United Kingdom by the Medical Research Council (MRC) and the Health Technology Assessment (HTA) programme between 1994 and 2002, and concluded that only 31% of trials achieved their planned recruitment target, and 45% did not recruit to within 80% of target. Furthermore, 54% of trials were awarded an extension to recruit, most with a supplementary grant.[165] Delays related to the central trial staff and local research staff were identified. It was found than 17 trials had pre-identified trial centres that did not participate as originally planned, for reasons such as funding problems and delays in the recruitment of trial staff. Internal problems for example with trial staff were also discussed as a factor contributing towards delays in later recruitment.

A number of strategies to improve recruitment have previously been identified by McDonald and colleagues; these include further promotion of the study (such as via newsletters or posters), changes to the inclusion criteria and protocol, and presentations to appropriate groups.[165] Recruitment strategies can therefore change as a result of pilot or feasibility phases of a study.

Sundaresen and colleagues described the concept of the ‘apparent recruitment fraction’ in their narrative discussion of an oncology trial’s recruitment progress, in contrast to the ‘true recruitment fraction’, as shown in box 14.[166]

Box 14. Apparent versus true recruitment fractions

Adapted from Sundaresan *et al.*'s 'Do screening trial recruitment logs accurately reflect the eligibility criteria of a given clinical trial? Early lessons from the RAVES 0803 trial' (2014)[166]

Apparent recruitment fraction = [number of patients recruited to the study] / [number who met the eligibility criteria and attended for assessment at a trial site]

True recruitment fraction = [number of patients recruited to the study] / [number of patients who satisfied the eligibility criteria, regardless of whether the attended an assessment at a trial site or not]

They have suggested that differences in the apparent and true recruitment fractions (33% versus 18% respectively, in their trial) can be improved through close collaboration with the referring clinicians, as screening or recruitment logs may not accurately represent the study's target population; patients with non-specific LBP or more than three months' duration may not necessarily be referred to the pain clinic from primary care, and are instead being managed by their GPs or referred to other specialists. A number of local GPs were identified and had given agreement to be involved and to aid recruitment, but were not represented at the trial management group meetings. This feasibility study has demonstrated the need for more primary care involvement at all stages of the study, from protocol design and patient screening and recruitment, to dissemination of the results.

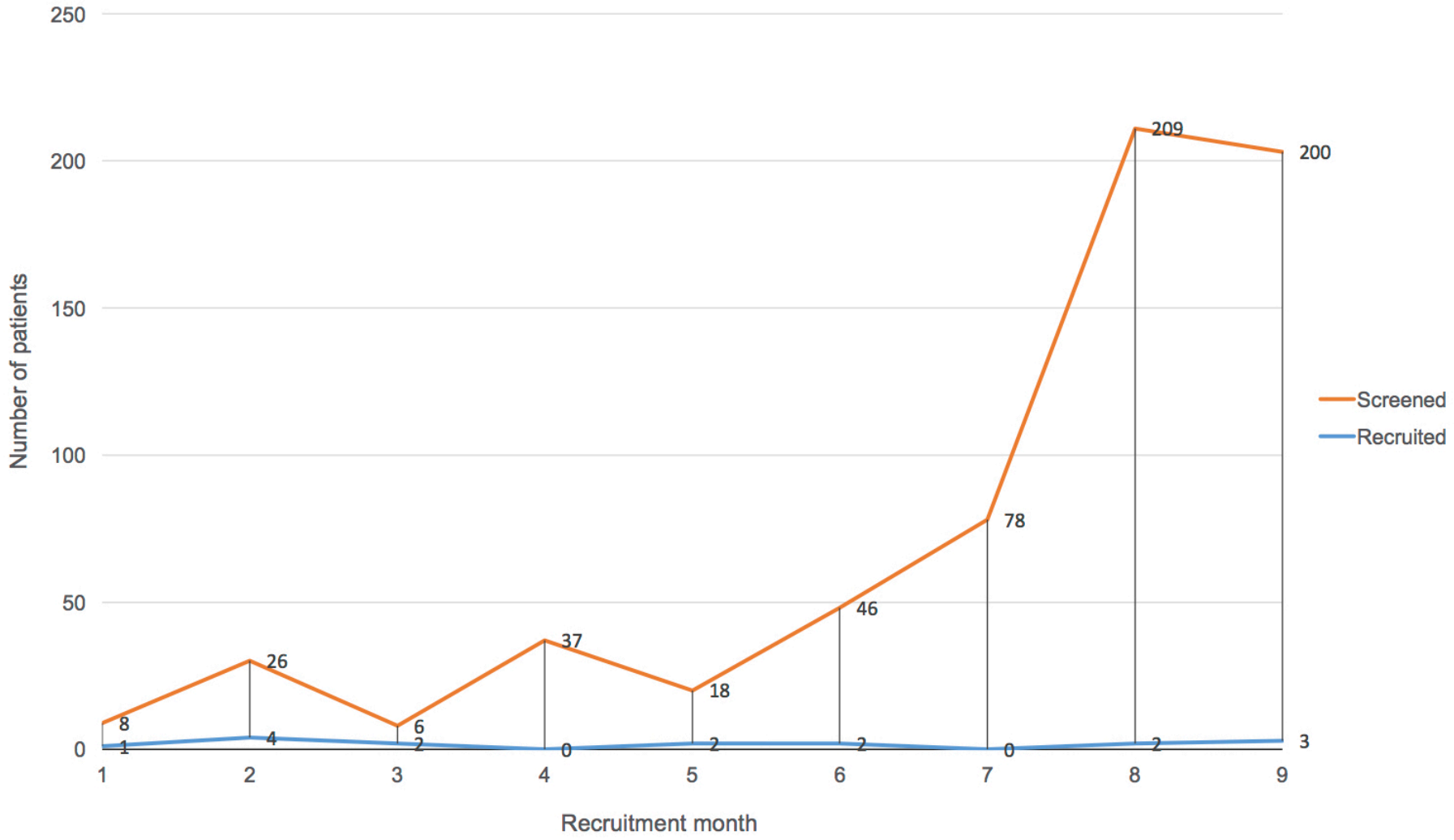
The trial co-ordinator kept and maintained a recruitment log which recorded anonymised details of all the patients who were screened for eligibility to enter the study, whether they were randomised or not. Details of ineligibility or non-participation were also recorded. Further analysis of the recruitment logs could be used to refine the protocol for future studies, for example by identifying certain inclusion or exclusion criteria which could potentially be modified to allow more patients to be eligible to enter the study. The reasons for ineligibility

to enter this study are detailed in table 11; these potentially modifiable barriers to recruitment, such as increasing or removing the upper age limit, should be reviewed prior to consideration of trial progression to a definitive study.

A retrospective audit at each of the three recruiting centres was carried out at the start of the feasibility study, to estimate a recruitment rate of eleven participants a week; five participants weekly from Barts Health NHS Trust, and three participants each from Basildon and Thurrock University Hospitals and The Walton Centre in Liverpool. This target was not met however at the single recruiting centre, as shown in appendix 8 which illustrates the actual versus the estimated numbers of participants recruited per week.

The feasibility study has shown that the greatest challenges to recruitment can largely be attributed to the patient population presenting to the hospital pain and spinal orthopaedic clinics, as an increase in the screening rate did not improve the rate of participant recruitment. The experiences of the research team can be used to guide future researchers to perhaps look elsewhere other than these clinics to recruit suitable participants. The patient population presenting to the pain and spinal orthopaedic clinics at Barts Health NHS Trust will be discussed later in this section.

Figure 17. Number of patients screened versus the recruitment rate, by recruitment month



Clinician and patient participation

Clinician participation in a study may be affected by time constraints, lack of staff and training, in addition to competing priorities during the study recruitment period, for example from involvement in other trials; these factors were identified by Prescott and colleagues in their systematic review paper 'Factors that limit the quality, number and progress of randomised controlled trials'.[167] Many of these factors also applied to the FACET feasibility study, where clinical staff recruited and consented participants from pain clinics alongside routine NHS work. The pain consultants involved in the study were all full-time clinicians and no additional time was allowed for the study interventions to take place, or for the consultant-led follow-up appointments which were often overbooked into routine clinical sessions. Based on the experiences of this study, a large-scale definitive trial may require substantial ring-fenced research time for any additional trial activity.

Patients attending the pain clinics at St Bartholomew's Hospital at Barts Health NHS Trust, located in Central London, are referred by their GPs via the NHS e-Referral Service (formerly Choose and Book) from a wide catchment area across the United Kingdom. A future definitive trial may consider remuneration of travel costs to increase attendance for study visits. A process evaluation could additionally be employed to look into other reasons that might affect compliance to the study protocol, such as work commitments or caring for dependents.

Schultz and Grimes have stated that 5% loss to follow-up is probably of little concern, whereas 20% or greater loss is likely to introduce a greater risk of bias in randomised trials, affecting the validity of the results.[168] A future trial may wish to compare the baseline characteristics of those participants who dropped out with those who completed the study, to identify the true effects of attrition within the study. The authors proposed a number of approaches to maximise participant follow-up, listed in box 15 below. Although the article was published in 2002, many of these factors remain relevant today and may need to be considered in any preliminary discussions of feasibility trial progression towards a definitive trial.

Suggested updates to maintain patient participation include the use of text message reminders or social media to return for study visits and follow-up appointments; however, as many text messaging platforms are not encrypted, this can limit what information can be sent to comply with information governance regulations. One Cochrane review on the use of text message reminders has shown that there is low to moderate quality evidence to support their use, as they can increase attendance at healthcare appointments compared to no reminders or postal reminders.[169] The Facet Injection Study used a text messaging system to collect daily and weekly pain scores with some degree of success, although a paper alternative was also recommended to improve compliance amongst older participants.[98]

More patient and public involvement at all stages of the research cycle could also help to recruit and retain participants in the study, for example by making the study protocol more acceptable and sensitive to those taking part, and by ensuring that the patient and public's interests and concerns remain the focus of the trial. The importance of patient and public involvement will be discussed further in this chapter.

Box 15. Proposals to maximise participant follow-up.

Adapted from Schulz and Grimes' 'Sample size slippages in randomised trials: exclusions and the lost and wayward' (2002)[168]

- Hire a person to manage and encourage follow-up
- Hire personnel to call participants or to visit participants at their home or place of work, if participants are not returning for follow-up
- Exclude before randomisation those likely to be unwilling to return
- Exclude before randomisation those likely to move
- Obtain contact information to prompt participants to return for follow-up and to facilitate location of participants if they do not return e.g. via mail, telephone, and e-mail for enrolled participants, for close friends or relatives who do not live with the participant, and for the participant's family doctor
- Obtain an identification number, such as a national healthcare number
- Establish follow-up venues suited to participants rather than to investigators and trial implementers e.g., more locations than just the central clinic or hospital, close to where participants live, convenient to access, and sensitive to waiting times
- Streamline trial procedures to move participants quickly through follow-up visits
- Keep data collection instruments short so as to not overburden the participant
- Provide excellent and free medical care
- Provide monetary subsidies, primarily for time and travel costs incurred by participants

Study population

The limited data shows that the patients screened for inclusion and presenting to pain clinics at Barts Health NHS Trust had high levels of disability related to their pain condition, often with co-existing psychological distress and low health-related quality of life. Approximately 1050 patients are referred to the pain clinics at St Bartholomew's Hospital each year as a new referral,[170] although many of these 'new' patients had already received spinal injections or surgery and were therefore ineligible to enter the study, as shown in table 11. Many of the patients referred to the spinal orthopaedic clinics also did not meet the study's entry criteria due to the presence of radicular pain, which could suggest pain of lumbar disc origin.

The Tower Hamlets Persistent Pain Services is located at Mile End Hospital and serves the population of the London Borough of Tower Hamlets in East London. Tower Hamlets is one of the most deprived boroughs in England with low average health deprivation scores, and has a diverse ethnic population with many residents born outside the United Kingdom.[171] One general practice-based survey within Tower Hamlets found that the commonest site of pain of those surveyed was in the low back, and that chronic widespread pain lasting for more than three months was more common and more severe in the Bangladeshi population compared to the White population.[172]

The reasons that no participants from Tower Hamlets were recruited to the study warrants further investigation even despite the small sample size; a future trial should make all efforts to include an adequate representation of the population, to make the results applicable and relevant. Translation and advocacy services are readily available for routine NHS visits, but not for non-NHS study-related visits. Previous researchers have shown that language barriers may affect an individual's decision to take part in a research study;[173] this however could be an area for further exploration in a future trial, for example by more patient and public involvement with representation from the South Asian population, to make the research more accessible to the diverse local population.

The highest proportion of participants recruited relative to the numbers screened was from the community pain clinic at the Essex Lodge GP surgery in Plaistow, East London, which is co-located within the GP surgery itself. Despite the very small sample size, it was observed that these patients were referred for specialist care earlier in their pain trajectory compared with the other recruiting clinics; this relative ease of referral to the pain services indicates that strong links and lines of communication between primary and secondary care is possible and feasible.

Trial management and mentoring

A trial manager or co-ordinator is essential for the delivery of high-quality trials; the NIHR Health Technology Assessment (HTA) programme has recommended that a dedicated trial manager is appointed to all clinical trials. The desirable qualities of a trial manager are detailed in the NIHR's generic job description for a clinical trials manager:

'The post holder will have the leading role in planning, co-ordinating and completing the project. They will have excellent communication and presentation skills, together with the ability to organise and motivate others. They will demonstrate flair, enthusiasm, innovation and leadership when faced with challenges and will provide strategic, tactical and operational management skills in the planning and execution of the project.'[174]

Successful trial delivery requires not only a well-designed trial from a scientific perspective, but also a structured, practical and business-like approach to its management. Farrell and colleagues have suggested that trials fail due to poor management, and that successful completion of a trial can be dependent on active management of every trial aspect.[175] Trials with a dedicated trial manager have been shown to have a higher chance of achieving the target sample size; the STEPS study found that trials with a dedicated trial manager had increased chances of successful recruitment (odds ratio 3.80, 98% confidence interval 0.79% to 36.14%, p value 0.087).[164]

A number of resources and support processes are available to provide guidance to trial managers in the United Kingdom. The on-line forum UKTMN Trial Managers' Network (http://www.tmn.ac.uk, last accessed 11th November 2017) seeks membership from trial managers of academic, non-commercial trials, to improve the delivery of high quality clinical trials within the United Kingdom by promoting best practice. The Trial Managers' Network (TMN) offers formal courses in clinical trial management, in addition to one day workshops. A professional accreditation scheme is in development.

The reference tool 'Trial Managers' Network Guide to Efficient Trial Management' has been produced by a group of volunteer TMN members.[176] The authors' objective was to produce an inclusive resource of trial management framework, providing pragmatic advice to those involved in clinical trial management. Currently in its fifth edition, this guide can be used as an induction tool for newly appointed trial staff and as a reference guide for more experienced trialists.

Prescott and colleagues have recommended, based on anecdotal evidence, that inexperienced trialists should be supported by experienced trialists.[167] A recent scoping literature review has identified mentorship as a key influence in the career progression of early career clinical academics; effective mentors were seen to provide moral and institutional support, leading to greater career satisfaction and confidence of the mentee.[177]

Strengths and limitations

Critical appraisal of systematic reviews

A critical appraisal is defined as the process of 'carefully and systematically examining research to judge its trustworthiness, and its value and relevance in a particular context.'[178] A strength of the critical appraisal of systematic reviews was in the methodology and in the composition of the review team; an

information specialist (librarian trained in systematic reviews) helped to develop the relevant search terms and search strategies, and two independent reviewers screened and assessed the retrieved articles. A third reviewer, acting as a tiebreaker, was available in case of disagreements. The primary reviewer had attended relevant training courses on systematic review methodology and software. The PRISMA-P guidelines were used as a basis for carrying out the search and presenting the results and discussion,[106] and the AMSTAR checklist, a validated measurement tool to assess the methodological quality of the systematic reviews, was applied independently by each assessor.[105]

It was originally intended to carry out a new systematic review and meta-analysis of lumbar facet joint injections for the management of LBP. However, a high quality systematic review had been published recently,[100] and an informal literature search revealed that very few relevant trials had been published in the intervening period. A weakness of the process was the inability to combine data from the randomised controlled trials identified from systematic reviews, as the studies were heterogeneous to provide any meaningful analysis.

The systematic review protocol was not prospectively registered. It is recommended that systematic review protocols with a health-related outcome are prospectively published in an international database such as the International Prospective Register of Systematic Reviews (PROSPERO); this would improve transparency and reduce any reporting bias, and avoid duplication of work.[179]

FACET feasibility study

The FACET feasibility study successfully addressed many of the study objectives, as detailed earlier in this chapter.

One strength of the study was the use of the modified Delphi survey to obtain a consensus amongst interventional pain specialists in the United Kingdom on the

procedural techniques including a sham procedure. No significant adverse events were reported as a result of the diagnostic medial branch blocks, lumbar facet joint injections and sham procedure, and the techniques themselves were reproducible. Some accuracy of assessment was demonstrated by the clinical team in determining pain of lumbar facet joint origin based on history and clinical examination alone, as shown by the positive response to diagnostic blocks in nine out of eleven participants (82%, 95% confidence interval 48% to 98%). Most the recruited participants were retained for the study's duration. However, the response to diagnostic injections and the attrition rate are imprecise due to the low number of participants recruited to the study.

CPP programme delivery was shown to feasible within the constraints of this single-centre study; it was delivered according to the protocol and all the study physiotherapists at each the three planned recruitment centres were trained to deliver the programme. However, the group sizes were smaller than anticipated; a more clinical- and cost-effective delivery could be achieved by having between six to ten participants per group, as shown in the BeST trial. This group size has been shown to be popular in clinical practice in that it allows for group discussion and problem solving.[83]

Good adherence to the statistical analysis plan has been demonstrated (see appendix 2); it was intended at the outset to present the available data by group, and not to carry out any formal statistical analyses. Although the data was limited due to small numbers of participants, it was deemed inappropriate to pool the data with other studies as no other published randomised controlled trials recruited from a comparable patient population with the same entry criteria and use of diagnostic block, and the previous trials have been of variable scientific quality (see figure 16). Other trials of lumbar facet joint injections have not tested the same hypotheses as different comparators have been used (usual care or physiotherapy instead of a sham procedure for example), with dissimilar techniques for the lumbar facet joint injections themselves described, no standardised sham or control injections, and different outcome measures. Pooling any limited data may increase the statistical precision of a definitive study by increasing the sample size and power, but only when used judiciously; combining heterogeneous studies could lead to flawed and misleading results.

In studies with a sham or placebo control, success in blinding can be better understood by the differences in correct guesses between the two groups.[180] None of the five participants in the active group correctly guessed their allocation, and one out of three participants who completed the study in the sham group correctly guessed their allocation. The blinded outcome assessor correctly guessed 4 out of 9 allocation groups (44.4%, 95% confidence interval 10% to 79%). This indicates some success in maintaining fidelity of blinding as a 50% accuracy is considered successful for a two-arm trial; however, the small sample size has resulted in wide confidence intervals which means that caution is advised when interpreting these results.

The study's main weakness was the failure to recruit sufficient participants from the pain and spinal orthopaedic clinics, which let to early closure by the funder and permission was not granted to open more than one recruiting site. The factors contributing to the slow study set-up, in particular in gaining research governance approvals, were largely out of the research team's control and have been detailed earlier in this chapter.

Although a patient representative was an original study co-applicant, another weakness of the study was the limited patient and public involvement once recruitment had commenced, beyond the initial set-up stage. The advantages of patient and public involvement and suggestions for a future trial are discussed in the following sections.

Amendments to the study protocol were made on the request of the newly-appointed trial monitor; this included the addition of inclusion criterion 6, 'Patients are suitable for the facet joint injections' and the re-wording of exclusion criterion 4, ''Red-flag' signs' (see boxes 2 and 3). Although the research team approved these changes to gain permission for recruitment to commence, the involvement of less experienced research staff at a later stage in the approvals process resulted in some potentially unnecessary and confusing additions to the inclusion and exclusion criteria.

Any results arising from this feasibility study should be interpreted tentatively as they may not be representative of a wider population; in addition to the small sample size, recruitment took place within secondary care only, from the pain clinics at Barts Health NHS Trust in London. Many of the patients seen in these clinics were not suitable, and it is possible that patients who would have met the entry criteria had not yet been referred from primary care services. The feasibility has identified several key areas which would benefit from a formal qualitative process evaluation; these are discussed in later in this chapter.

Implications for clinical practice and policy

A recent report by The King's Fund, an independent charity with the aim of improving health and care in England, has investigated the financial pressures on the NHS (largely attributed to a slowing down in funding growth over recent years) and has identified additional independent factors that affect the access and quality of patient care.[181] These factors affecting healthcare services and patient care (in terms of access and quality) can also be applied to the commissioning process of lumbar facet joint injections for chronic LBP management, and include spending decisions at a national and local level, workforce capacity, ongoing service development, patient choice, the use of targets and guidelines to regulate and manage performance, the use of new technologies, marketing incentives, and patient demand.

Clinical Commissioning Groups (CCGs) were set up in England in 2012 with a statutory duty to improve the quality of NHS services, and an aim of obtaining the best possible health outcomes at a local level. The 2013 National Pain Audit has already identified stark variations across England in patient care and outcomes.[10] It can also be seen that variations in CCG funding of facet joint injections in secondary care exist, which change with emerging and updated guidelines; for example, the Bristol, North Somerset and South Gloucestershire CCGs Commissioning Group did not routinely fund facet joint injections following the publication of NICE clinical guideline CG88,[42, 182] and in line with NICE guideline NG59,[25] do not routinely fund facet joint injections but will give

approval, based on certain criteria, to fund for single diagnostic medial branch blocks and radiofrequency denervation.[183] Treatments that are not routinely funded by the CCGs require an NHS England Individual Funding Request which is completed by a clinician on behalf of a patient in 'exceptional clinical circumstances'.[184]

The 2013 document 'Pain management services: planning for the future' was produced by the Royal College of Physicians and endorsed by the British Pain Society, Chronic Pain Policy Coalition and Faculty of Pain Medicine of the Royal College of Anaesthetists; this publication aimed to give support and guidance to clinicians, in particular those leading pain management services, to appropriately engage with commissioners in order to provide optimal services.[185] The stakeholders have highlighted pain as a commissioning priority and propose that each CCG has a duty to consult experts in the services it commissions. The results of the FACET feasibility study and critical appraisal of systematic reviews may therefore be taken forward in any discussion of local pain services commissioning, as high quality evidence to support the use of lumbar facet joint injections in LBP management remains lacking, and there are no published studies of cost-effectiveness.

Implications for future research

Critical appraisal of systematic reviews

The heterogeneity demonstrated across the existing randomised controlled trials of facet joint injections, in terms of scope and quality, indicate that there is no indication at present to carry out an updated or *de novo* systematic review; a future systematic review must however combine new and existing data from randomised controlled trials, in order to provide definitive evidence to guide clinical practice.

Drawing on the strengths and limitations of previous systematic reviews, the composition of any review team should be taken into consideration; any future multidisciplinary review group must involve appropriate expertise and experience, consisting of experts in interventional pain management in addition to experts in systematic review methods, relevant evidence searching and quantitative methods. Patient and public involvement could help to focus the research question, improving its clinical relevance. A team leader, with knowledge of protocol implementation, may be required to facilitate the review process.[186]

Heterogeneity within the patient population was frequently cited as a reason for inability to carry out data synthesis. Some reviewers subdivided the studies according to the comparator, or therapeutic agent used. The updated method guideline for systematic reviews in the Cochrane Back and Neck Group has included mandatory and optional recommendations for review authors based on new methodological evidence; a homogenous population is recommended for inclusion in a future review, with the type of back or spinal disorder clearly described. This group also advised on the inclusion of comparators with a clear contrast for the index intervention, to independently assess the effects.[119]

Amundsen and colleagues have reported heterogeneity of the entry criteria of non-specific LBP randomised controlled trials in their systematic review of trials

published between 2006 and 2012.[187] This diversity amongst trials was noted even between studies of similar populations, and was cited as a contributing factor towards the difficulties of carrying out between-trial comparisons. Consistent use of their suggested inclusion and exclusion criteria in future trials could result in studies of homogeneous populations that would allow for pooling of results in meta-analyses.

The research recommendations for the future systematic review are summarised in box 16 below.

Box 16. Research recommendations: the future systematic review

- The review team needs appropriate expertise and experience
- Steps must be taken to minimise methodological and reporting bias and to improve transparency, by using relevant checklists and method guidelines for systematic reviews
- The systematic review protocol should be prospectively registered with an international database
- Future high quality systematic reviews of randomised controlled trials intra-articular lumbar facet joint injections are required to objectively summarise the evidence for decision makers

FACET feasibility study

The two research teams funded by NIHR to answer the research question, 'Is a definitive study to assess the effectiveness and cost-effectiveness of facet joint injections compared to best non-invasive care for people with persistent non-specific low back pain feasible?' were led by Professor Martin Underwood, University of Warwick,[97] and Professor Richard Langford, Barts Health NHS Trust.[96] The two trial protocols are compared in table 18 below.

Table 18. Comparison of the FACET feasibility study and Facet Feasibility study protocols

	FACET feasibility study (Langford team)[99]	Facet Feasibility study (Underwood team)[122]
Primary objective	To assess the feasibility of conducting a definitive trial to evaluate the clinical- and cost-effectiveness of lumbar facet joint injections compared to a sham procedure, in patients with non-specific LBP of more than 3 months' duration	To explore the feasibility of running a randomised controlled trial to test the clinical and cost-effectiveness of intra-articular lumbar facet joint injections in addition to best usual non-invasive care
Trial design	Multicentre (3 sites) Double-blind randomised controlled trial 2 arms – intervention (facet joint injections + best usual care) versus control (sham + best usual care)	Multicentre (up to 6 sites) Non-blinded randomised controlled trial 2 arms – intervention (facet joint injections + best usual care) versus control (best usual care only)
Inclusion criteria	LBP of three months' or greater duration At least 2 components of NICE-recommended best non-invasive care completed, including education and one of a physical exercise programme, acupuncture, or manual therapy	LBP for at least six months Has had registered health-professional delivered treatment for LBP in the past 2 years No radicular symptoms

	FACET feasibility study (Langford team)[99]	Facet Feasibility study (Underwood team)[122]
Exclusion criteria	Previous spinal injections or spinal surgery Other dominant pain, or widespread pain Radicular pain	Previous spinal injections or spinal surgery Corticosteroid usage in the preceding 3 months
Estimated sample size	60 participants	150 participants
Recruitment period	6 months	6 months
Diagnostic criteria	Diagnostic lumbar facet medial branch nerve injections with lidocaine – a positive response is a 50% or greater pain reduction lasting for over 30 minutes	Physiotherapist assessment (based on agreed criteria following a consensus conference)[64]
Outcome measures	6 weeks, 3 months and 6 months post randomisation Pain intensity and characteristics, use of co-analgesics, early withdrawal from study, expectation of benefit, health-related quality of life, functional impairment, satisfaction with treatment, complications	3, 6 and 12 months post randomisation Medications, satisfaction with health state, troublesomeness questionnaire, back pain-related disability, back pain severity, psychological distress, pain self-efficacy, health-related quality of

	FACET feasibility study (Langford team)[99]	Facet Feasibility study (Underwood team)[122]
	and adverse events, co-psychological well-being, healthcare utilisation and costs	life, health utilities, well-being, current work status, health and social service resource use
Follow-up period	6 months post randomisation	12 months post randomisation
Usual care components	CPP programme delivered by study physiotherapists using the Back Skills Training Programme Initial 1-hour one-to-one session after the intervention, followed by between 4 and 6 90 minute sessions with 2 study physiotherapists in small groups	Bespoke package of physical and behavioural rehabilitation tailored to individual patients Initial 1-hour session prior to intervention, followed by 5 30 minute one-to-one sessions with a study physiotherapist
Intervention group	4 lumbar facet joints injected at 2 bilateral lumbar levels 0.5 ml 0.5% bupivacaine + 20 mg methylprednisolone (1 ml total volume) per joint	Up to six lumbar facet joints injected 1 ml 0.5% bupivacaine + 1 ml triamcinolone 10 mg (2 ml total volume) per joint
Comparator	Sham procedure – 4 peri-articular injections at 2 bilateral lumbar levels 0.5 ml normal saline per site	'Best usual care package'

The target recruitment rate was not met by either of the two research teams funded by the NIHR HTA programme to investigate the feasibility of carrying out a definitive study assessing the use of lumbar facet joint injections for persistent non-specific LBP, with both groups experiencing significant delays in study set-up; Professor Underwood's team recruited 26 participants (the study aimed to recruit approximately 150 participants) and the FACET feasibility study randomised 9 participants (60 participants were expected to be randomised). Professor Underwood's team has concluded that a definitive study to explore the addition of facet joint injections to usual care is indeed feasible, but that recruitment from the pain clinics alone was insufficient.[98] The FACET feasibility study has concluded that a definitive study comparing facet joint injections to a sham procedure is potentially feasible, with adjustments in the target population and increased primary care involvement, to screen patients earlier in their pain trajectory.[99] Some considerations for future research are detailed below.

Future trial designs

An evaluation of the two failed feasibility studies calls for an assessment of the study designs themselves. A trial comparing usual care only to the addition of facet joint injections, the trial design used in Professor Underwood's study,[100] could allow for a more pragmatic evaluation, by providing evidence of improved effectiveness of an intervention over best existing practice that already been endorsed by national guidelines. The comparison of an active intra-articular injection with a sham procedure in a double-blinded randomised controlled trial design, as utilised by Professor Langford's team,[99] may be considered more scientifically rigorous,[188] with the advantage that established best usual care could also be provided to both groups. The authors of the superseded Cochrane review of injection therapy for chronic LBP management proposed that placebo-controlled trials of spinal injections should be a priority over trials that compared injections to other treatments, and that future randomised controlled trials must be methodologically sound with more focus on long-term treatment effects (Nelemans).[111] However, large sample sizes may be necessary to detect any effect size due to variations between and within the groups.

In 2003, Horng and Miller published an ethical framework on the use of sham procedures in clinical trials; the authors stated that the use of a sham control is often methodologically necessary to show that any outcome changes can be attributed to the active procedure itself and not due to its mode of administration or a placebo response due to study participant's expectations and psychosomatic effects.[189] The risks of the sham procedure itself must however be taken into consideration, and need to be justified in any well-conducted study.

A published systematic review of LBP trials has shown that placebo-controlled trials can give biased results; the use of placebos that are potentially not inert, and a failure to achieve acceptable blinding were a common finding in these trials where an imperfect placebo was used.[180] The use of a two-arm trial may not control for any improvement in LBP due to its natural history i.e. any improvement seen in both groups could be unrelated to the treatment allocation.

A future trial could consider the use of a three-arm trial design, simultaneously comparing lumbar facet joint injections, a sham procedure, and usual care (no injections). Such a trial would allow the following research questions to be addressed: whether facet joint injections are superior to a sham procedure, and whether facet joint injections are superior to usual care. A three-arm trial could also for the first time in a trial of facet joint injections compare a sham treatment against usual care in a homogeneous population.

The findings of such a study could be more scientifically relevant and statistically robust as it would demonstrate any associations between the groups with a greater degree of reliability than a two-arm trial. Any independent effects from the different allocation groups could potentially be evaluated, and any outcome changes due to the natural history and progression of LBP and other incidental factors are controlled for. Selection from a homogeneous patient population by utilising standardised inclusion and exclusion criteria, as suggested by Amundsen and colleagues, would also allow for further comparisons with other future trials utilising the same guidelines for trial entry.[187]

Another future research direction could be the evaluation of lumbar facet joint medial branch radiofrequency denervation procedures, as the current evidence for their use has similarly been muddled by flawed study design and the inclusion of a heterogeneous patient population in trials and meta-analyses of radiofrequency denervation. The use of diagnostic injections to more accurately diagnose pain of lumbar facet joint origin is another area for future researchers to consider as there remains no clear consensus on what medicinal product to inject, how many blocks are required, and what a positive response should be. However, despite these controversies, the latest NICE guidance recommends consideration for assessment for radiofrequency denervation those with a positive response to a diagnostic medial branch block; the referral criteria are detailed further in table 1.[25]

Use of a consensus approach

Both the Langford and Underwood teams utilised a consensus approach to decide on the technique for lumbar facet joint injections. Professor Langford's group carried out a web-based survey of approximately 250 interventional pain specialists in the United Kingdom, of whom 42 took part. The questions and answer choices were pre-determined in an early trial management group meeting (see appendix 4), and the final decisions were made by the trial management group members. Professor Underwood's team published a transparent and inclusive approach by inviting professionals and lay people with an interest in LBP management to attend a one-day conference, which took the form of a nominal group technique where fourteen different aspects of injection technique were discussed.[64] Fifty-two people attended on the day, of whom nineteen with pain consultants and physicians. The uncertainty about the injectate was later resolved by email (eleven responses).

Future reviewers may wish to consider a true Delphi method to gain consensus on the injection techniques, where questionnaires are answered anonymously by expert panellists then fed back to the researchers. This technique may have advantages in this area with limited research and lack of clarity, by involving national and international experts in LBP management as panellists for a more

accurate representation of 'expert consensus'. The process also means that the views of stronger panellists do not necessarily dominate the process. Based on the experiences of Professor Underwood's team, experts in finalising the consensus will be required.[64]

Patient and public involvement

The involvement of patients and members of the public can improve the quality and relevance of clinical research, by providing personal knowledge and experience of the medical condition under investigation, and a different viewpoint.[190] The INVOLVE programme is a national advisory group set up in 1996 to support greater public involvement in the NHS, public health and social care research in England; the group defines public (this term includes patients, potential patients, carers, healthcare users and relevant representing organisations) involvement as research carried out 'with' or 'by' members of the public, as opposed to 'to', 'about' or 'for' them.[191] Patient and public involvement is increasingly a requirement to receive funding and is considered best practice; the INVOLVE programme has recommended a number of ways that the public can be involved in the research process, from identifying and prioritising the research topic to commissioning the study, involvement in the design and running of the trial itself, undertaking the research (for example in highlighting the findings that are most relevant to the public), dissemination of results, implementing the research, and evaluating its impact.

A future definitive trial must therefore consider stronger patient and public involvement at all stages of the research cycle. This could include the early appointment of a study co-applicant as a lead for public involvement and recruiting members of the public to help identify research priorities and as members of the trial steering committee; these members could be identified via the hospital pain clinics or GP practices, and through organisations such as the British Pain Society's Patient Liaison Committee, and Back Care (the National Back Pain Association). Members of the public could also be asked to comment on questionnaire design and on the participant information sheets, to make the research as appropriate and accessible as possible. Members of the

public could also be consulted on how best to report and disseminate the research findings.

Recruitment sites and primary care collaboration

The choice of recruitment site was dictated by the funders, who requested in the commissioning brief that recruitment should take place in 'secondary care centres, e.g. pain or orthopaedic, possibly also primary care'.[96] Both feasibility studies have shown that in the current climate in the United Kingdom, it is not possible to recruit sufficient patients meeting the eligibility criteria from such secondary care clinics.

An evaluation of the recruitment methods and recruiting sites of other trials may be required; for example, the thirteen randomised controlled trials of lumbar facet joint injections identified from the systematic review papers in chapter 2 recruited a median of 80 participants per study (this ranged from 18 to 120). One recently published study of radiofrequency denervation published in the Netherlands recruited 251 patients to the facet joint arm; the relatively large number of participants recruited could be attributed the suspension of all regular national reimbursement programmes due to the absence of rigorous scientific evidence, meaning that only those who took part in the study would receive these interventional pain procedures.[77] Furthermore, only those who had a positive response to a diagnostic block would be reimbursed. This may have contributed towards a selection bias and a relatively high positive responder rate to the diagnostic block.[80] The FACTS study was a multicentre comparative-effectiveness study in the United States comparing facet joint injections with medial branch blocks and a placebo injection, recruiting 229 participants between March 2014 and August 2017.[192] Both studies had relatively lax entry criteria which could have produced smaller effect sizes; their results may therefore not apply to real-world conditions or an NHS setting.

The current guidance in the United Kingdom does not recommend lumbar facet joint injections for chronic LBP management;[25] patients with persistent LBP who have not responded to conservative treatment may therefore only be offered these injections as part of a research study. A future study should consider

recruitment from GP practices and musculoskeletal physiotherapy services alongside hospital pain clinics; a definitive study should therefore build in a pilot phase to estimate the screening to recruitment ratio from this patient population, with pre-defined criteria for study progression i.e. an acceptable screening to recruitment ratio. Other feasibility outcomes, including an estimation of the outcome standard deviations to inform a power calculation, and an accurate assessment of blinding, could also be answered by this pilot study.

Future researchers must engage with GP practices and commissioners for any future collaborative work, for example working alongside the Trauma Programme of Care Board Pathfinder Project (where spinal injections are not recommended)[41]; potential participants, for example those with high levels of disability, may benefit from such interventions and rehabilitation at an early stage and could be identified and considered for inclusion in a trial without having to be first referred to a pain or spinal orthopaedic clinic. Some feasibility of this process has already been demonstrated by the Facet Injection Study, referrals were later being taken directly from physiotherapy departments and from primary care in order to improvement the recruitment rate.[98] A parallel process evaluation (see below) would be essential to recognise any contextual factors that might affect the implementation and outcomes of patients recruited from primary care, compared to those recruited from hospital clinics.

Process evaluation

The Medical Research Council (MRC) produced guidance on the evaluation of complex interventions in 2000, which was updated in 2008 and has called for a researchers to provide a more definitive evaluation of processes as well as outcomes in their studies.[193, 194] Although a process evaluation was not proposed as part of this feasibility study, it is hoped that the preparatory work may pave the way for a future definitive study which would incorporate a parallel process evaluation alongside an evaluation of outcomes. Moore and colleagues, on behalf of the MRC Population Health Science Research Network, defined a process evaluation as:

‘A study which aims to understand the functioning of an intervention, by examining implementation, mechanism of impact, and contextual factors. Process evaluation is complementary to, but not a substitute for, high quality outcomes evaluation.’[195]

The guidance, which draws on evidence from literature reviews, consultation with stakeholders and case studies, offers a number of key recommendations in the planning, design, analysis and conduct of a process evaluation. These recommendations could be included in a definitive trial proposal by utilising a mixed-methods approach incorporating both quantitative (including structured observations and self-report questionnaires) and qualitative (one-to-one interviews and groups interviews or focus groups) methods. It is increasingly being recognised that trial success is dependent on the context and environment, as well as the intervention being tested; a process evaluation could further allow researchers and analysts to explore the definitive trial’s fidelity of implementation and adherence to the study protocol, and to identify any possible predictors or mediators of change.

Professor Underwood’s team did carry out a formal process evaluation of patient experience within their trial; although the data may not have been fully representative due to low patient numbers, the researchers were able to describe in detail the reasons for slow recruitment, and insight was gained into some aspects of study implementation.

One area for further exploration highlighted by the FACET feasibility study was the long duration of pain awareness amongst all the study participants (mean 6.8 years, see table 14), which could indicate the time taken to be referred from primary care to specialist centres. The feasibility study also showed 34 out of fifty eligible patients declined to take part, and five of the remaining sixteen dropped out after giving consent (figure 11). Incorporating a parallel process evaluation into the study protocol, with regulatory approvals in place to contact patients once they have left the study, could explore these reasons for study drop out in more details. A process evaluation could also be used to improve the quality of outcome data by exploring the reasons into why some questionnaire datasets were incomplete or spoiled, and whether the use of

injection therapy might improve compliance with a CPP programme. Furthermore, this process could explore with more formality the acceptability of the two treatment arms (active facet joint injection with steroid, versus a sham procedure) to both study participants and research clinicians, using structured questionnaires.

The MRC has stated that the guidance for complex intervention evaluation will be jointly updated with NIHR in 2019, due to significant developments in the field.

Research recommendations

The research recommendations for a future definitive study are summarised in box 17.

Box 17. Research recommendations: the future definitive study

- A definitive trial is feasible with adjustments to the target population
- A definitive trial needs to draw on lessons learned from both teams and involve future collaborations between the research groups
- One proposed trial design is a three-arm trial comparing facet joint injections, a sham procedure and usual care
- An internal pilot phase, with pre-defined criteria for progression, could assess whether patients in primary care are more suitable for trial inclusion than those referred for specialist care
- Future researchers should utilise standardised inclusion and exclusion criteria to reduce heterogeneity in the study population
- A parallel process evaluation should be incorporated into the protocol and consent for follow-up from all participants should be obtained at trial entry
- Future definitive trials of intra-articular injections and radiofrequency denervation in the management of chronic low back pain are required

Chapter 6: Conclusions

The existing evidence to support the use of facet joint injections is equivocal and the published research findings are controversial, with methodological variability detected across the studies and reviews. Fundamentally flawed research has caused confusion and disappointment to researchers, commissioners and patients themselves. As it is not possible to summarise the evidence, which currently consists of both good and poor quality research, there remains a future need for high quality randomised controlled trials in a homogeneous population, incorporating the latest trial methods which would lead towards a new systematic review with meta-analyses. Any emerging research therefore has the potential to change the recommendations for the management of persistent non-specific LBP at a national and international level.

Despite the equivocal evidence to support their use, both intra-articular facet joint injections and radiofrequency denervation of their medial branch nerves are currently being offered to selected patients with persistent non-specific LBP in the United Kingdom at the time of writing. However, some Clinical Commissioning Groups (CCGs), who are decision makers responsible in England for the planning and commissioning of local healthcare services, have classified lumbar facet joint injections as a 'procedure of limited clinical value'; lumbar facet joint injections are therefore no longer being routinely funded by certain CCGs due to financial constraints on the NHS. It is very possible that their future use may be restricted to research studies only.

CCGs are currently routinely funding for radiofrequency denervation, on the recommendation on the 2016 NICE guidelines, to those patients with persistent LBP who have had a positive response to a single diagnostic block and who have not responded to more conservative management.[25] However, some of the published trials of radiofrequency denervation including those used in guideline development have been criticised for poor methodology, for example their inclusion of a heterogeneous population; there additionally remains no consensus on the definition of a 'positive diagnostic block', and no high quality evidence for their long-term clinical- and cost-effectiveness.

The FACET feasibility study met many of the intended feasibility objectives but failed to achieve the target recruitment rate. Lessons have been learnt here, which can be used to guide future definitive studies of facet joint injections and radiofrequency denervation. Based on the experiences of both feasibility studies, one proposed trial design which could more accurately reflect best usual practice is a three-arm pragmatic comparative effectiveness trial comparing facet joint injections with a sham procedure and usual care. The successful elements of both teams should be built upon in a future collaboration combining national and international expertise, for example incorporating the recruitment enhancement strategies and consensus methodology. Embedding an internal pilot phase into a definitive trial could aid in optimising the recruitment sites by investigating whether suitable participants can be screened earlier in their pain trajectories from GP surgeries and primary care-based musculoskeletal physiotherapy services. The addition of a parallel process evaluation could provide invaluable information on whether certain aspects of the research cycle can be improved, and by exploring any barriers in the referral pathway from primary to secondary care.

The FACET feasibility study did not set out to answer the research question, 'Are lumbar facet joint injections with steroid superior to a sham procedure in the management of persistent non-specific low back pain?', but instead aimed to explore the feasibility of carrying out a definitive study within an NHS setting. Lumbar facet joint injections for the management of chronic LBP may indeed be proven to be financially and clinically justifiable in selected patients, by adding value and improving quality of life, but the evidence remains lacking. The thesis has however identified key areas in chronic LBP management that require further exploration; future research must however focus not only on high quality clinical trials, but also on methodologically robust systematic reviews and meta-analyses which have the potential to inform clinical practice and alter current healthcare policies.

Appendix 1. Search strategies for the literature search of systematic reviews and meta-analyses of randomised controlled trials of intra-articular lumbar facet joint injections for chronic low back pain management

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

Medline (date range searched: 1966 to 6th February 2017)

#	Database	Search term	Results
1	Medline	exp *LOW BACK PAIN/	13733
2	Medline	("low back pain").ti,ab	21120
3	Medline	exp *ZYGAPOPHYSEAL JOINT/	961
4	Medline	("facet joint").ti,ab	2227
5	Medline	exp *CHRONIC PAIN/ OR exp *PAIN/	218391
6	Medline	(lumbar OR paravertebral).ti,ab	91494
7	Medline	exp *LUMBAR VERTEBRAE/	26956
8	Medline	1 OR 2	24954
9	Medline	3 OR 4	2683
10	Medline	6 OR 7	98948
11	Medline	5 AND 10	9560

12	Medline	8 OR 9 OR 10 OR 11	117090
13	Medline	exp *INJECTIONS, INTRA-ARTICULAR/	809
14	Medline	("intra articular*").ti,ab	12196
15	Medline	(facet ADJ2 injection).ti,ab	143
16	Medline	(facet ADJ2 joint).ti,ab	2299
17	Medline	exp *FLUOROSCOPY/	5060
18	Medline	(fluoroscop*).ti,ab	21046
19	Medline	exp *THERAPEUTICS/	2895415
20	Medline	(therap*).ti,ab	2169176
21	Medline	("percutaneous spinal").ti,ab	94
22	Medline	13 OR 14	12630
23	Medline	15 AND 16	120
24	Medline	17 OR 18	23098
25	Medline	19 OR 20	4590592
26	Medline	exp *INJECTIONS/	20026
27	Medline	(injection*).ti,ab	496795
28	Medline	26 OR 27	505646
29	Medline	21 AND 28	7
30	Medline	22 OR 23 OR 24 OR 25 OR 29	4610334
31	Medline	12 AND 30	49755
32	Medline	("systematic review*").ti,ab	94141
33	Medline	31 AND 32	1138

34	Medline	("meta analysis").ti,ab	88442
35	Medline	31 AND 34	521
36	Medline	("control* trial*" OR RCT).ti,ab	13597
37	Medline	31 AND 36	179
38	Medline	33 OR 35 OR 37	1504
39	Medline	(facet).ti,ab	10869
40	Medline	32 AND 39	123

Embase (date range searched: 1966 to 6th February 2017)

#	Database	Search term	Results
1	EMBASE	exp *LOW BACK PAIN/	23697
2	EMBASE	("low back pain").ti,ab	28245
3	EMBASE	exp *ZYGAPOPHYSEAL JOINT/	509
4	EMBASE	("facet joint").ti,ab	2999
5	EMBASE	exp *CHRONIC PAIN/ OR exp *PAIN/	386200
6	EMBASE	(lumbar OR paravertebral).ti,ab	123427
7	EMBASE	exp *LUMBAR VERTEBRAE/	7855
8	EMBASE	1 OR 2	35444
9	EMBASE	3 OR 4	3251
10	EMBASE	6 OR 7	125759
11	EMBASE	5 AND 10	16010
12	EMBASE	8 OR 9 OR 10 OR 11	151862

13	EMBASE	exp *INJECTIONS, INTRA-ARTICULAR/	1884
14	EMBASE	("intra articular*").ti,ab	15071
15	EMBASE	(facet ADJ2 injection).ti,ab	193
16	EMBASE	(facet ADJ2 joint).ti,ab	3056
17	EMBASE	exp *FLUOROSCOPY/	6811
18	EMBASE	(fluoroscop*).ti,ab	34353
19	EMBASE	exp *THERAPEUTICS/	3002010
20	EMBASE	(therap*).ti,ab	3111511
21	EMBASE	("percutaneous spinal").ti,ab	138
22	EMBASE	13 OR 14	16232
23	EMBASE	15 AND 16	165
24	EMBASE	17 OR 18	35845
25	EMBASE	19 OR 20	5235530
26	EMBASE	exp *INJECTIONS/	33580
27	EMBASE	(injection*).ti,ab	635413
28	EMBASE	26 OR 27	639110
29	EMBASE	21 AND 28	11
30	EMBASE	22 OR 23 OR 24 OR 25 OR 29	5270243
31	EMBASE	12 AND 30	38627
32	EMBASE	("systematic review*").ti,ab	118882
33	EMBASE	31 AND 32	867
34	EMBASE	("meta analysis").ti,ab	117968

35	EMBASE	31 AND 34	428
36	EMBASE	("control* trial*" OR RCT).ti,ab	231428
37	EMBASE	31 AND 36	2362
38	EMBASE	33 OR 35 OR 37	2906
39	EMBASE	(facet).ti,ab	12624
40	EMBASE	32 AND 39	149

Cochrane Central Register of Controlled Trials (date range searched: 1966 to 6th February 2017)

ID	Search
#1	MeSH descriptor: [Back Pain] explode all trees
#2	back near pain
#3	dorsalgia
#4	back disorder*
#5	backache
#6	MeSH descriptor: [Low Back Pain] explode all trees
#7	(lumbar next pain)
#8	(#1 or #2 or #3 or #4 or #5 or #6 or #7)
#9	MeSH descriptor: [Zygapophyseal Joint] explode all trees
#10	facet near joints
#11	zygapophysial*
#12	(#9 or #10 or #11)
#13	(#8 and #12)

Appendix 2. Statistical analysis plan

Date: 14th June 2016
Version number: 1.1

A multicentre double-blind randomised controlled trial to assess the clinical- and cost-effectiveness of facet-joint injections in selected patients with non-specific low back pain: a feasibility study.

Statistical Analysis Plan (SAP)

Trial short title	Facet-joint feasibility study
Trial registration number	ISRCTN12191542
Trial chief investigator	Dr Vivek Mehta
Trial manager	Ms. Alia Ahmad
Trial statistician	Prof Rod Taylor
SAP author	Prof Rod Taylor
CTU involvement (name of CTU and role, e.g. data management, randomisation)	PenCTU (data management, randomisation)

Date of SAP	SAP version number	Date presented to Trial management group/Trial steering committee	Significant amendments since previous version	Date approved
14th June 2016	1.1			

1. Abbreviations and definitions

Abbreviation	Full terminology/definition

2. Statistical guidelines

Analyses are to be conducted in accordance with International Conference on Harmonisation (ICH) statistical guidelines for clinical trials and Consolidated Standards for Reporting Trials (CONSORT) reporting checklist for trials [1,2].

3. Trial background

Pain of lumbar facet-joint origin is a common cause of low back pain in adults [3], and may lead to chronic pain and disability, with associated health and socioeconomic implications. At present there is no definitive research to support the use of targeted lumbar facet-joint injections (FJIs) to manage this pain. Due to the lack of high quality, robust clinical evidence the National Institute for Health and Care Excellence (NICE) clinical guidelines published in 2009 did not recommend injections of therapeutic substances into the back for non-specific low back pain [3], despite their potential to reduce pain intensity and rehabilitation. As a result, NICE called for further research to be undertaken to clarify the clinical effectiveness and cost-effectiveness of interventional pain procedures for the treatment of low back pain.

Before undertaking a definitive trial to assess clinical effectiveness and cost effectiveness of FJIs compared to sham (placebo) procedure for non-specific low back pain, there are a number of questions that first need to be within this a feasibility study. The facet-joint feasibility study (reference number HTA - 11/31/02) is an NIHR HTA programme funded project.

This statistical analysis plan (SAP) relates to the Study Protocol Version 6, 25th April 2016.

4. Trial information

4.1 Interventions

Facet-joint injection (FJIs) (intervention) or sham injection (control).

4.2 Phase of trial

Single feasibility stage.

The definitive trial will be deemed feasible if: successful standardisation of the method of injection and the test-run of the sham procedure, study design is deemed acceptable by patients and clinicians, and able to recruit and retain sufficient patients.

4.3 Randomisation level

Patients will be randomised on 1:1 ratio to intervention and control groups using minimisation to ensure between group balance by centre and baseline pain scores.

4.4 Study design

Two-arm parallel randomised controlled trial. Administration of injections will be carried out by the operator (the site's Principal Investigator) who cannot be blinded. Patients and all other members of the research visits, including research nurse performing outcome assessments, will be blinded. Randomisation will take place following provision of informed consent and provision of baseline data. Follow-up data collection will take place at 6 weeks, and 3 and 6 months post-randomisation.

4.5 Purpose of the analyses

As this is a feasibility study, it is not proposed to formally inferentially test differences in outcomes or costs between or within the groups. The purposes of the statistical analyses are as follows:

1. to report recruitment rates (and 95% confidence intervals)
2. to provide descriptive summarises of baseline and follow up data for all outcomes;
3. to report attrition rates (and 95% confidence intervals) at all follow-up time points;
4. to report individual data missingness at all follow-up timepoints;
5. to provide descriptive data on adverse events.

4.6 Sample size calculation

A total of 60 patients will be recruited (equally allocated to either intervention and control groups). Assuming a 20% attrition rate, we expect 24 full data sets per arm will be completed at the end of the study. This sample size will allow us to achieve our various feasibility objectives. For example, 60 patients gives the ability to estimate the precision of our assumed attrition rate with error of error of ±5% at 95% confidence level and 24 patients per arm is acceptable for a reasonable estimate of variance of outcomes [4].

4.*7 Study populations*

Full inclusion/exclusion criteria are set out in the protocol.

5. Study objectives and endpoints

5.1 Aims and objectives

The study aim is to assess the feasibility of conducting a definitive trial to evaluate the clinical- and cost-effectiveness of facet-joint injections compared to a sham procedure, in patients with non-specific low back pain of more than three months' duration.

Specific objectives are:

1. To assess the eligibility criteria, recruitment and retention of patients in the two treatment arms (FJI versus sham procedure) by
   a. Assessing the feasibility of recruitment in the three centres, with regards to a potential definitive trial.
   b. Reviewing the number of completed patient data sets.
   c. Auditing the quality of data entry at the centres.
   d. Assessing and analysing any protocol violations (such as failure to deliver the combined physical and psychological programme), side effects and other adverse outcomes.
2. To assess the feasibility and acceptability of the two treatment arms from the point of view of patients and their pain teams.
3. To assess the feasibility of the proposed definitive trial design including:
4. Testing of randomisation and blinding procedures.
5. Development of an appropriate active and sham procedure for FJIs.
6. Assessment of the consistency of the trial sites to deliver the combined physical and psychological programme.
7. Ability to collect the outcomes proposed for the main trial (pain, functioning, health-related quality of life, anxiety and depression, health care resource utilisation, complications, and adverse events).
8. To estimate outcome standard deviation to inform the power calculation for a definitive trial.
9. To finalise the protocol design, statistical plan, number of centres required and study duration of the definitive trial.

5.2 Endpoints

Endpoints, with their source and time points collected, are set out in Table 3.

Table 3. Outcomes

Endpoint	Scoring	Source	Timepoints collected
Brief Pain Inventory [BPI] (Short Form)	Continuous	2 domains • BPI severity • BPI interference Each 0-10	Baseline, 6 weeks, 3 months, 6 months
Short-form McGill Pain Questionnaire (SF-MPQ-2)	Continuous	3 pain domains • Sensory • Affective • Total Each 0-10	Baseline, 6 weeks, 3 months, 6 months
EQ-5D-5L	Continuous	Single total utility score (-0.594 to 1.000)	Baseline, 6 weeks, 3 months, 6 months
12-item Short Form Health Survey (SF-12)	Continuous	2 domains • Physical component score (PCS) • Mental component score (MCS) Both 0-100	Baseline, 6 weeks, 3 months, 6 months
Oswestry Low Back Pain Disability Questionnaire	Continuous	8 items • pain intensity • personal care • walking/running sitting, standing sleeping • traveling Each scored 8-48	Baseline, 6 weeks, 3 months, 6 months
Pain Self Efficacy Questionnaire (PSEQ)	Continuous	Single score Score 0-60	Baseline, 6 weeks, 3 months, 6 months
Hospital Anxiety and Depression Score (HADS)	Continuous	2 domains • HADS anxiety • HADS depression Both scored 0-21	Baseline, 6 weeks, 3 months, 6 months
Pain Catastrophizing Scale (PCS)	Continuous	• Total (0-52) & 3 subscales rumination (0-16) • magnification (0-12) • helplessness (0-24)	Baseline, 6 weeks, 3 months, 6 months
Stanford Presenteeism Scale	Continuous	Single scale Score 6-30	Baseline, 6 weeks, 3 months, 6 months
Satisfaction with treatment scale	???	???	6 weeks, 3 months, 6 months
Expectation of benefit scale	???	???	Baseline

5.3 Derived variables

No analyses of derived variables are planned.

6. General analysis considerations

6.1 Timing of analyses

All analyses will be performed following collection of data at 6 months , and finalisation and tidying of the database. No interim analyses are planned.

6.2 Types of analyses

The descriptive analysis of primary and outcomes at baseline and follow up will based on the intention to treat analysis, i.e. according to initial random allocation) using complete case data. .

6.3 Covariates and subgroups

No covariate adjustment or subgroup analyses will be reported. Baseline characteristics of both groups will presented descriptively with no inferential comparison of groups.

6.4 Presentation of inferential analyses

Not relevant.

6.5 Missing data

The level of data missingness for each outcome will be reported for both groups at each of the 3 assesssment points. No imputation of missing data will be performed.

6.6 Adverse events

Data on serious adverse events will be set out descriptively by group.

6.7 Reporting conventions

Quantiles, such as the median, or minimum and maximum, will be reported to the same number of decimal places as the original data. The mean, standard deviation and other statistics will be reported to one decimal place greater than the original data. .

6.8 Mediation analyses

No mediational analysis will be conducted

6.9 Execution of analyses

The initial ITT analyses will be performed by a statistician who is blinded to intervention allocation.. All analyses will be performed using Stata v.14.1.

8. Tables and figures

Proposed dummy tables and figure templates are shown in the Appendix.

9. References

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *Statistical Principles for Clinical Trials.* Guideline E9. 1998. http://www.ich.org/LOB/media/MEDIA485.pdf
2. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet.* 2001. 14;357:1191-4.
3. Savigny P, Kuntze S, Watson P, et al. *Low back pain: early management of persistent non- specific low back pain.* London: National Collaborating Centre for Primary Care and Royal College of General Practitioners. May 2009. (NICE clinical guideline 88, www.nice.org.uk/CG88)
4. Browne RH. On the use of a pilot sample for sample size distribution. *Stat Med.* 1995;14: 1933-1940.

10. Appendix

Figure 1. CONSORT study patient flow

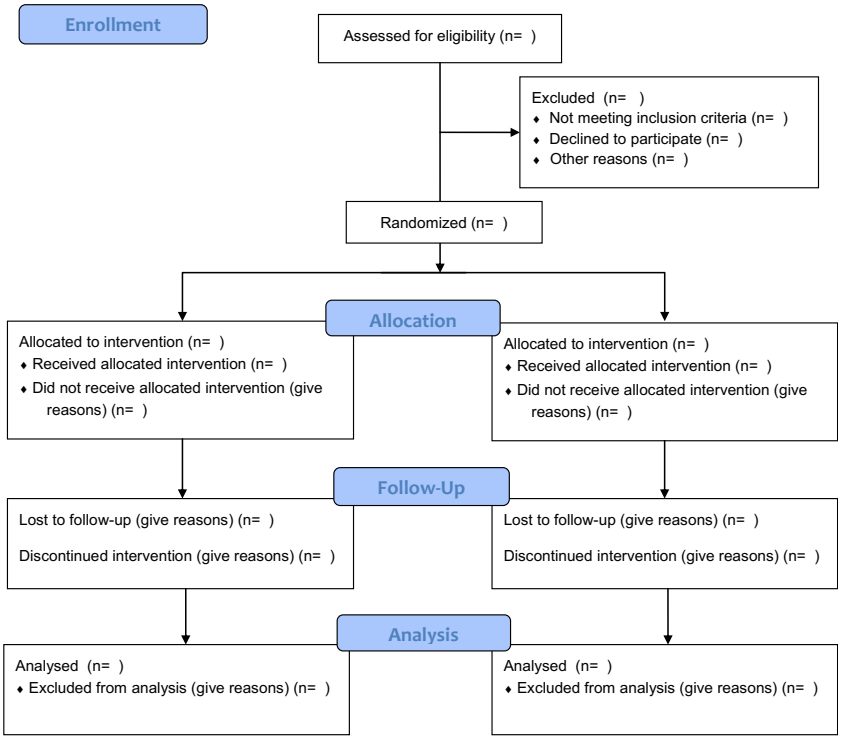


Table 1. Summary of patient baseline characteristics and outcomes

	Intervention	Control
Characteristics		
Gender, % male		
Age, mean (standard deviation)		
[etc]		
Outcomes		
Expectation of benefit scale		
Brief Pain Inventory (Short Form)		
Short-form McGill Pain Questionnaire (SF-MPQ-2)		
EQ-5D-5L		
12-item Short Form Health Survey (SF-12)		
Oswestry Low Back Pain Disability Questionnaire		
Pain Self Efficacy Questionnaire (PSEQ)		
Hospital Anxiety and Depression Score (HADS)		
Pain Catastrophizing Scale (PCS)		
Stanford Presenteeism Scale		

Table 2. Summary of descriptive outcomes at all follow up points

	6-weeks N Mean (SD)		3-months N Mean (SD)		6-months N Mean (SD)	
	Intervention	Control	Intervention	Control	Intervention	Control
Brief Pain Inventory (Short Form)						
Short-form McGill Pain Questionnaire (SF-MPQ-2)						
EQ-5D-5L						
12-item Short Form Health Survey (SF-12)						
Oswestry Low Back Pain Disability Questionnaire						
Pain Self Efficacy Questionnaire (PSEQ)						
Hospital Anxiety						

and Depression Score (HADS)						
Pain Catastrophizing Scale (PCS)						
Stanford Presenteeism Scale						
Satisfaction with treatment scale						
Expectation of benefit scale						

Table 3. Complications and adverse events up to 6-months

	Intervention	Control
Complication 1		

Appendix 3. Participant information sheet

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

PARTICIPANT INFORMATION SHEET

Title of study: A multicentre double-blind randomised controlled trial to assess the clinical- and cost-effectiveness of facet-joint injections in selected patients with non-specific low-back pain: a feasibility study

Principal Investigator: Dr Saowarat Snidvongs

REC reference: 15/LO/0500

EudraCT number: 2014-003187-20

Version 6.1 25th August 2016

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and healthcare professionals if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Low back pain is common in adults, and may lead to chronic disability. Lumbar facet-joints are small, paired joints in the low back that provide stability, integrity and flexibility of movement to the spine. Diseased facet-joints may cause persistent low back pain.

Although the pain may be treated with targeted facet-joint injections, there is currently no high quality or definitive clinical evidence to support their use. The National Institute for Health and Care Excellence (NICE) therefore do not currently support the use of lumbar facet-joint injections in treating low back pain due to the lack of high quality evidence.

This is a preliminary study to see whether it is feasible to conduct a larger definitive trial to assess lumbar facet-joint injections (a needle is inserted into the facet-joint and steroid injected) by comparing it to a dummy or 'sham' procedure (a needle is inserted near the facet-joint but no therapeutic substance injected).

The purpose of a feasibility study is to help researchers decide whether the intervention (lumbar facet-joint injections for low back pain) is appropriate for further testing in a larger definitive trial.

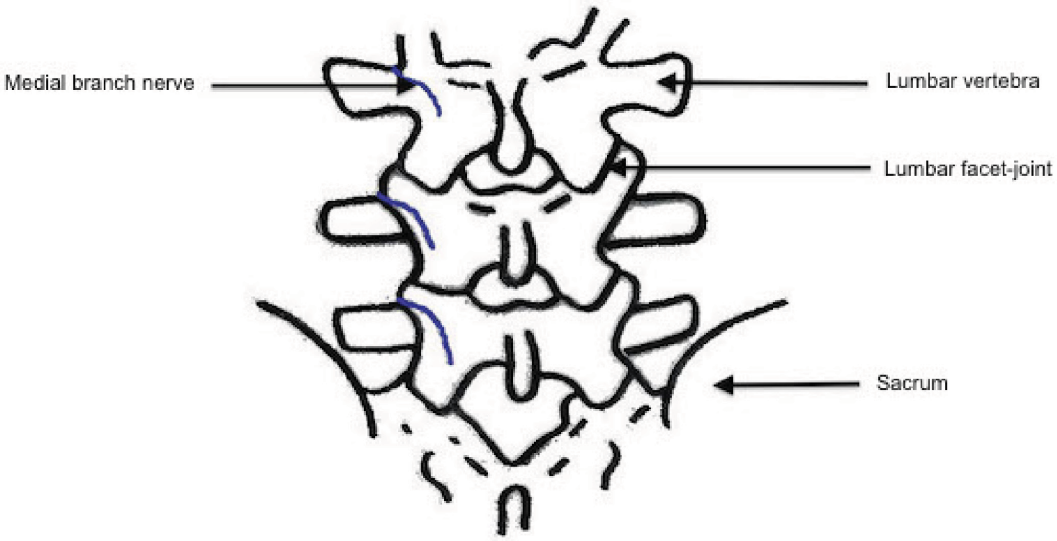


Diagram of the lower part of the vertebral column or backbone

Why have I been chosen?

You have been chosen because you have been referred to the pain clinic with low back pain of greater than three months' duration that may be of facet-joint origin. The pain has not improved despite best non-invasive care as recommended by NICE (pain education, and one or more of the following: physical education programme, acupuncture, and manual therapy).

Do I have to take part?

The decision to participate in this study is entirely up to you. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form; you are still free to change your mind and may withdraw from the study at any time and without

giving a reason. A decision to withdraw from the study at any time will not affect the standard of care that you receive now or in the future.

If you do decide to withdraw from the study, we will retain any data obtained prior to withdrawal. We will not collect any further data from you in relation to this study. You will be followed-up in the pain clinic as part of usual NHS practice.

What will happen to me if I take part?

You will first receive an appointment to have a diagnostic test for lumbar facet-joint disease. This is an injection of local anaesthetic into your low back to block the painful nerve supply to the facet-joints (medial branch nerve block). Depending on your response, you may receive a second appointment to return for either the facet-joint injections or a sham procedure. You will have an equal chance of being in either group.

The sham procedure is a 'dummy' injection near to, but not in, the facet-joint with a saline solution (no drug action). This is a necessary part of the study design, as it will enable the two procedures to be compared. You will not know whether you have been given facet-joint injections or a sham procedure, as this has been shown to be one of the best ways we have for knowing what the intervention (lumbar facet-joint injections for low back pain) really does.

An expert, who is a Consultant in Pain Medicine and the Principal Investigator at your site, will carry out all the injections. The procedures will take place in a dedicated sterile environment, such as an operating theatre in a hospital day surgery unit. You will lie on your front awake for the duration of the injections, which usually take no more than 20 to 30 minutes to complete. You will go home on the same day.

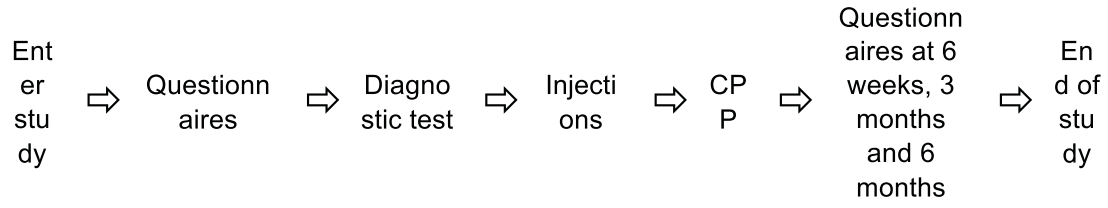
You will be invited to attend six sessions of a combined physical and psychological programme (CPP) after your injections. These will be delivered to you in small groups by a trained physiotherapist and each session will last for 90 minutes. The CPP has been recommended by NICE as a strategy to reduce pain and its impact on day-to-day life, even if the pain cannot be cured completely.

You will be required to attend six separate hospital or clinic appointments, in addition to the CPP. The first three appointments are with a Consultant in Pain Medicine and are part of routine clinical practice (initial consultation, diagnostic test, and facet-joint injections or sham procedure).

There are three follow-up visits with a research nurse after your injections, which will take place in a research clinic to complete a set of questionnaires relating to your pain and

health-related quality of life. You will complete four sets of questionnaires in total (before the injections, and 6 weeks, 3 months and 6 months after the injections).

The study will end when you complete your final set of questionnaires, six months after the injections.



What are the side effects of taking part?

The diagnostic injections and facet-joint injections are commonly performed and considered safe. The procedures may be uncomfortable but are not considered painful, and are generally well tolerated with you being awake. You may experience a brief stinging sensation when we numb your skin with a local anaesthetic. The same applies for the sham procedure group.

Minor side effects from the diagnostic injections and facet-joint injections are not uncommon and include bruising at the site of injection. Other complications include technical failure (we are unable to perform the procedure), failure to relieve pain, injury to nerves, and infection. Major complications are extremely rare.

Ionising radiation in the form of x-rays will be used in both groups – this is necessary to allow the needles to safely enter the correct space in your back. Exposure to ionising radiation increases the risk of incurring cancer in later life. The radiation dose received has been assessed by a medical physics expert and is considered to be of very low risk, comparable to about 2 months of background (environmental) radiation exposure.

What are the possible disadvantages of taking part?

There are no disadvantages in taking part in this study although it may take some time (up to an hour) to complete the questionnaires. If you are in the sham group, you are not expected to obtain any pain relief from your procedure but you will be followed-up in the pain clinic by a Consultant in Pain Medicine and offered further treatment to manage your pain as required, including facet-joint injections.

What are the possible benefits of taking part?

If you are in the treatment group and receive lumbar facet-joint injections, you may experience symptomatic relief of your low back pain. If you are in the sham group, there may be no direct benefit to you but we anticipate that the results of the study could benefit future patients with low back pain, by increasing their treatment options.

What if more information becomes available?

Sometimes during the course of a research study, new information becomes available about the treatment or medicine being studied. We will inform you of any new developments should this occur.

What happens if there is a problem?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you. If you wish to complain formally, you can do this through the NHS complaints procedure. Details of this can be obtained from the Patient Advice and Liaison Service [insert local details here].

Will my taking part be kept confidential?

Your confidentiality will be safeguarded during and after the study, with data handling, processing and storage carried out according to the Data Protection Act 1998. Any individual data will be anonymised and given a research code, and all paper data will be stored in a locked cabinet within a locked office in the Pain and Anaesthesia Research Centre at Barts Health NHS Trust in London. Electronic data will be stored on a password-protected computer accessed only by members of the research team. The data generated by the study will be entered by the research team onto an electronic database developed by the Peninsula Clinical Trials Unit, and will be analysed confidentiality at the University of Exeter by Professor Rod Taylor the study statistician.

Regulatory authorities and the study Sponsor may also look at the study data, to ensure that the study is being carried out correctly.

Involvement of your general practitioner

With your permission, your GP will be informed that you are taking part in this study. We may contact your GP prior to contacting you during the study to make sure your personal circumstances have not changed since our last contact.

What will happen to the results of the research study?

The results of the study will be entered onto a database by the research team at the Pain and Anaesthesia Research Centre at Barts Health NHS Trust, and analysed with statistical advice from the University of Exeter.

The results will be published in a report upon completion of the study, and may be made available to you on request. It is anticipated that the study will run for 21 months. You will not be identified in any report or publication.

Who is funding the research?

This study has received a grant from the National Institute for Heath Research (NIHR), which is funded through the Department of Health in the UK to improve the health and wealth of the nation through research.

Who has reviewed this study?

This study has been reviewed by the NHS Research Ethics Committee London – City & East. The National Research Ethics Service protects the rights, safety, dignity and wellbeing of research participants.

The study drugs have authorisation for use from the Medicines & Healthcare products Regulatory Agency (MHRA). The MHRA regulates medicines and medical devices in the UK.

The study has also been reviewed by the NIHR to meet the necessary scientific standards.

Contact details for further information:

If you have any general questions on taking part in research, please contact the Patient Advice and Liaison Service [insert local details here]. The research team can also be contacted directly [insert local details here].

Site Principal Investigator: [details to be inserted here]

Site lead research nurse: [details to be inserted here]

Thank you for considering taking part in this study.

Appendix 4. Delphi exercise

Pain specialists in the United Kingdom took part in a modified Delphi survey to agree on the choice of steroid, volume of injectate into the facet joint, and site of placement of the needle for the sham procedure (see table 19). There were forty-two responders out of approximately 250 pain specialists consulted.

Table 19. Results of the Delphi exercise

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

Question	Response (%)	Response count
1. At what maximum steroid dose, do you think, reviewers and general sceptics could claim that a positive result for a facet-joint injection was due to systematic action, rather than local benefit?		
60 mg of methylprednisolone	25.0	10
80 mg of methylprednisolone	22.5	9
100 mg of methylprednisolone	20.0	8
120 mg of methylprednisolone	32.5	13

	Response (%)	Response count
2. Which volume is closest to your choice in each facet-joint?		
< 1 ml	28.6	12
1 ml	38.1	16
1.5 ml	21.4	9

	Response (%)	Response count
3. Assuming that we keep to a maximum of four joints, what steroid dose should we use in each joint?		
10 mg of methylprednisolone per joint	40.5	17
20 mg of methylprednisolone per joint	57.1	24
30 mg of methylprednisolone per joint	2.4	1

	Most likely, % (*n*)	Likely, % (*n*)	Not likely, % (*n*)	Does not affect the outcome, % (*n*)	Rating average	Response count
4. If we were not to use methylprednisolone, which of these two steroids would you prefer?						
Triamcinolone	85.7 (36)	9.5 (4)	2.4 (1)	2.4 (1)	1.21	42
Dexamethasone	12.5 (4)	34.4 (11)	50.0 (16)	3.1 (1)	2.44	32

	Response (%)	Response count
5. The sham group should have a fluoroscopic guided needle placed		
Next to the periarticular surface with no injection	38.1	16
Next to the periarticular surface with saline injected (same volume as the active group)	28.6	12
Intra-articular placement with only contrast injected	21.4	9
Intra-articular placement with contrast and placebo (saline) injection (same volume as the active group)	11.9	5

Appendix 5. Sample case report form

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

Patient identification number _____

Patient initials _____

Barts Health NHS Trust

Barts and The London School of Medicine and Dentistry

CASE REPORT FORM

A multicentre double-blind randomised controlled trial to assess the clinical- and cost-effectiveness of facet-joint injections in selected patients with non-specific low back pain: a feasibility study.

Short title: Facet-joint feasibility study

Sponsor: Barts Health NHS Trust

Representative of the Sponsor:

Dr Sally Burtles

Director of Research Services

JRMO

QM Innovation Building

5 Walden Street

London

E1 2EF

Phone: 020 7882 7265

Email: sponsorsrep@bartshealth.nhs.uk

Chief investigator: Dr Vivek Mehta

Site principal investigator:

Co-investigators:

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Patient eligibility – inclusion criteria

Inclusion criteria		
	Yes	No
1. Patient aged 18 to 70 years attending pain clinics identified during routine clinical assessment of non-specific low back pain		
2. Low back pain of greater than three months' duration		
3. Average pain intensity score of 4/10 or more in the seven days preceding recruitment despite NICE recommended treatment		
4. Dominantly paraspinal (not midline) tenderness at two bilateral lumbar levels		
5. At least two components of NICE-recommended best non-invasive care completed, including education and one of a physical exercise programme, acupuncture, and manual therapy		
6. Patient is suitable for the facet- joint feasibility study		

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Patient eligibility – exclusion criteria

Exclusion criteria		
	Yes	No
1. Patient refusal to consent		
2. More than four painful lumbar facet-joints		
3. Patient has not completed at least two components of NICE-recommended best non-invasive care, including education and one of a physical exercise programme, acupuncture, and manual therapy		
4. 'Red flag' signs including thoracic pain, fever, unexplained weight loss, bladder or bowel dysfunction, progressive neurological deficit, and saddle anaesthesia		
5. Hypersensitivity to study medications		
6. Dominantly midline tenderness over the lumbar spine, any other dominant pain or radicular pain.		
7. Any major systemic disease or mental health illness that may affect the patient's pain, disability and/or their ability to exercise and rehabilitate, as judged by the Principal Investigators		
8. Any active neoplastic disease, including primary or secondary neoplasm		
9. Pregnant or breastfeeding		
10. Previous lumbar facet-joint injections, spinal surgery or any major trauma or infection to lumbar spine.		
11. Patient with morbid obesity (body mass index of 35 or greater)		
12. Participation in another clinical trial of a investigational medicinal product or disease related intervention in the past thirty days		
13. Patient unable to commit to the six-month study duration		
14. Patient involved in legal actions or employment or benefit tribunals related to their low back pain		
15. Patient with a history of substance abuse		

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Consent

Date of patient consent _____

Version of consent form used _____

Baseline pain score (NRS) up 7 days preceding recruitment ☐ date taken:

I confirm that this patient is eligible to enter the study _____

(signature of medical doctor on delegation log)

Patient visit schedule

		Date of visit(s)
Visit 1	Screening and informed consent Outcome questionnaires at baseline	
Visit 2	Diagnostic test (medial branch nerve blocks)	
Visit 3	Study procedure (facet-joint injections or sham procedure)	
	Combined physical and psychological programme	Date of first session: Date of last session: Number of sessions attended:
Visit 4	Outcome questionnaires at 6 weeks	
Visit 5	Outcome questionnaires at 3 months	
Visit 6	Outcome questionnaires at 6 months	

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Patient history

To be completed by research assistant

General health

How long has the patient been aware of his/her non-specific low back pain? _____ Years _____ Months

In general, would the patient describe his/her health as: (tick box)

- Excellent ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐

Occupation information

What is the patient's current work status? (tick box)

- Full time ☐
- Part time ☐
- Volunteer ☐
- Modified duties ☐
- Disabled ☐
- Not working ☐
- Homemaker ☐
- Retired ☐
- Not applicable ☐

Type of work or occupation: _____

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Patient history

To be completed by research assistant

Did the patient's illness cause him/her to stop working?

- Yes ☐
- No ☐
- Not applicable ☐
- Other (give reason): _____

If the patient continued working, how many work days in the past 3 months, prior to the procedure, did he/she miss due to pain? _____ days

What was the patient's level of activity prior to the procedure?

- Hard manual work ☐
- Lifting ☐
- Walking ☐
- Sedentary ☐

Social history

Smoking

- Current smoker ☐ _____ cigarettes/day
- Ex-smoker ☐ _____ date stopped
- Never smoked ☐

Alcohol

_____ Units consumed per week

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Patient history

To be completed by research assistant

Exercise per week: (tick box)	>5 days	☐
	3-5 day	☐
	1-2 days	☐
	Less than 1 day	☐

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Visit 1

Baseline

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Patient questionnaire

To be completed by research assistant

Treatments/hospitalisations/medications

Has the patient seen a healthcare professional within the past 4 weeks due to pain?

_____ Emergency department visits

_____ Length of stay in hospital

_____ GP appointments

_____ pain clinic

Other (give details):

_____

Current analgesics (name of medication, dosage and frequency)

Other medications (name of medication, dosage and frequency)

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Patient's expectation of benefit

How much improvement in pain does the patient expect from the procedure? (circle one)

1	2	3	4	5	6

Expect no improvement Expect total improvement

Outcome questionnaires

Has the questionnaire pack (set 1) been completed? Yes ☐

No ☐

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Visit 2

Diagnostic test

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Diagnostic test (medial branch nerve blocks)

To be completed by PI

Study centre	_____	
Date of procedure	_____	
Time of procedure	_____	
Operator	_____	
Procedure details	Number of injections	_____
IMP injected	1% lidocaine 0.5% per site	
	Levels injected	

Post injection evaluation 1 (20 to 40 minutes after injection)

To be completed by PI

Time of evaluation _____

Minutes after injection _____

Please rate the patient's current level of pain on a numerical rating scale (NRS) of 0-10. (0 is no pain and 10 is worst pain):

Patient's current pain score = ☐

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Post injection evaluation 2 (180 to 240 minutes after injection)

To be completed by PI

Time of evaluation _____

Minutes after injection _____

Please rate the patient's current level of pain on a numerical rating scale (NRS) of 0-10. (0 is no pain and 10 is worst pain):

Patient's current pain score = ☐

Investigator decision: **positive test is a 50% or greater pain relief lasting more than 30 minutes** (circle one)

☐ Positive (for randomisation) **Date of randomisation** _____

☐ Negative (end of study)

Visit 3- Study procedures form the 'blinded CRF'

This section is to be completed by the PI and kept separately in a locked filing cabinet until unblinding

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Blinded CRF

Barts Health NHS Trust

Barts and The London School of Medicine and Dentistry

CASE REPORT FORM

A multicentre double-blind randomised controlled trial to assess the clinical- and cost-effectiveness of facet-joint injections in selected patients with non-specific low back pain: a feasibility study.

Short title: Facet-joint feasibility study

Sponsor: Barts Health NHS Trust

Representative of the Sponsor:

Dr Sally Burtles

Director of Research Services

JRMO

QM Innovation Building

5 Walden Street

London

E1 2EF

Phone: 020 7882 7265

Email: sponsorsrep@bartshealth.nhs.uk

Chief investigator: **Dr Vivek Mehta**

Site principal investigator:

This section is the 'blinded CRF' to be completed by the PI and kept separately in a locked filing cabinet until unblinding

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Blinded CRF

Visit 3

Study procedure

Study procedure (facet-joint injections or sham procedure)

To be completed by PI

Study centre _____

Date of procedure _____

Time of procedure _____

Operator _____

Procedure details

Number of injections _____

Levels injected

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Combined physical and psychological programme

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Combined physical and psychological programme

Study centre _____

	Date attended	Outcomes delivered Y/N
Session 1	_____	Y/N
Session 2	_____	Y/N
Session 3	_____	Y/N
Session 4	_____	Y/N
Session 5	_____	Y/N
Session 6	_____	

If all outcomes not delivered please provide further details:

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Outcomes

6 Weeks Post Intervention

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Patient questionnaire

To be completed by research assistant

Treatments/hospitalisations/medications

Has the patient seen a healthcare professional within the past 4 weeks due to pain?

_____ Emergency department visits

_____ Length of stay in hospital

_____ GP appointments

_____ pain clinic

Other (give details):

_____

Current analgesics (name of medication, dosage and frequency)

Other medications (name of medication, dosage and frequency)

Patient's expectation of benefit

Investigator's initials _____

Date _____

Visit 4 – Outcome measures at 6 weeks

Patient identification number _____

Patient initials _____

How satisfied is the patient with the treatment received? (circle one)

0	1	2	3	4	5	6	7	8	9	10

Extremely dissatisfied Extremely satisfied

Outcome questionnaires

Has the questionnaire pack (set 2) been completed? Yes ☐

No ☐

Adverse events

Have there been any adverse events since the intervention? Yes ☐

No ☐

If yes, please complete the adverse event log at the end of the CRF

Changes to medications

Have there been any changes in medication since the intervention? Yes ☐

No ☐

If yes, please complete in box below:

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Outcomes

3 Months Post Intervention

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Patient questionnaire

To be completed by research assistant

Treatments/hospitalisations/medications

Has the patient seen a healthcare professional within the past 4 weeks due to pain?

_____ Emergency department visits

_____ Length of stay in hospital

_____ GP appointments

_____ pain clinic

Other (give details):

_____

Current analgesics (name of medication, dosage and frequency)

Other medications (name of medication, dosage and frequency)

Patient's expectation of benefit

Investigator's initials _____

Date _____

Visit 5 – Outcome measures at 3 months

Patient identification number _____

Patient initials _____

How satisfied is the patient with the treatment received? (circle one)

0	1	2	3	4	5	6	7	8	9	10

Extremely dissatisfied Extremely satisfied

Outcome questionnaires

Has the questionnaire pack (set 3) been completed? Yes ☐

No ☐

Adverse events

Have there been any adverse events since the last visit? Yes ☐

No ☐

If yes, please complete the adverse event log at the end of the CRF

Changes to medications

Have there been any changes in medication since the last visit? Yes ☐

No ☐

If yes, please complete in box below:

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Outcomes

6 Months Post Intervention

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Patient questionnaire

To be completed by research assistant

Treatments/hospitalisations/medications

Has the patient seen a healthcare professional within the past 4 weeks due to pain?

_____ Emergency department visits

_____ Length of stay in hospital

_____ GP appointments

_____ pain clinic

Other (give details):

_____

Current analgesics (name of medication, dosage and frequency)

Other medications (name of medication, dosage and frequency)

Patient's expectation of benefit

Investigator's initials _____

Date _____

Visit 6 – Outcome measures after 6 months

Patient identification number _____

Patient initials _____

How satisfied is the patient with the treatment received? (circle one)

0	1	2	3	4	5	6	7	8	9	10

Extremely dissatisfied Extremely satisfied

Outcome questionnaires

Has the questionnaire pack (set 4) been completed? Yes ☐

No ☐

Adverse events

Have there been any adverse events since the last visit? Yes ☐

No ☐

If yes, please complete the adverse event log at the end of the CRF

Changes to medications

Have there been any changes in medication since the last visit? Yes ☐

No ☐

If yes, please complete in box below:

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

End of study

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

End of study

To be completed by research assistant

Date of final study contact with patient _____

Reason (circle one)

- ☐ Completed study
- ☐ Withdrawn from study
- ☐ Other

Reason for withdrawal from study (circle one)

- ☐ Drop out
- ☐ Protocol non-compliance
- ☐ Adverse event (please complete AE form at the end of the CRF)
- ☐ Other

If other, provide further details:

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Adverse events

Investigator's initials _____

Date _____

Patient identification number _____

Patient initials _____

Adverse events 1

Date adverse event occurred _____

Date investigator become aware of the event _____

Location of adverse event

_____

Event details:

Is the adverse event related to the procedure? (circle one only)

- ☐ Unrelated
- ☐ Unlikely
- ☐ Possible
- ☐ Probably
- ☐ Related

Investigator's initials _____

Date _____

End of study

Patient identification number _____

Patient initials _____

Was the adverse event a serious adverse event (SAE)?

- ☐ Yes
- ☐ No (move on to action plan)

Serious criteria (circle all that apply)

- ☐ The AE led or could have led to a congenital anomaly/birth defect
- ☐ The AE led or could have led to death
- ☐ Resulted in medical or surgical intervention to prevent permanent impairment to a body structure
- ☐ Life-threatening illness or injury
- ☐ Resulted in permanent impairment of a body structure or body function
- ☐ Required inpatient hospitalisation
- ☐ Other

Action plan

- ☐ No action required
- ☐ Amend consent form
- ☐ Amend protocol
- ☐ Inform current subjects
- ☐ Terminate or suspend protocol
- ☐ Other

Has the Sponsor been informed?

- ☐ Yes
- ☐ No

If other, provide further details:

Investigator's initials _____

Date _____

End of study

Patient identification number _____

Patient initials _____

Adverse events 2

Date adverse event occurred _____

Date investigator become aware of the event _____

Location of adverse event

_____

Event details:

Is the adverse event related to the procedure? (circle one only)

- ☐ Unrelated
- ☐ Unlikely
- ☐ Possible
- ☐ Probably
- ☐ Related

Investigator's initials _____

Date _____

End of study

Patient identification number _____

Patient initials _____

Was the adverse event a serious adverse event (SAE)?

- ☐ Yes
- ☐ No (move on to action plan)

Serious criteria (circle all that apply)

- ☐ The AE led or could have led to a congenital anomaly/birth defect
- ☐ The AE led or could have led to death
- ☐ Resulted in medical or surgical intervention to prevent permanent impairment to a body structure
- ☐ Life-threatening illness or injury
- ☐ Resulted in permanent impairment of a body structure or body function
- ☐ Required inpatient hospitalisation
- ☐ Other

Action plan

- ☐ No action required
- ☐ Amend consent form
- ☐ Amend protocol
- ☐ Inform current subjects
- ☐ Terminate or suspend protocol
- ☐ Other

Has the Sponsor been informed?

- ☐ Yes
- ☐ No

If other, provide further details:

Investigator's initials _____

Date _____

Appendix 6. Sample adverse event log

Reproduced from Snidvongs *et al.*'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]

ReDA number 008021 BLT
REC number 15/LO/0500
EudraCT number 2014-003187-20

CI: Vivek Mehta
Study name: Facet- Joint Study
IMP used in trial: Depo-Medrone, Bupivicaine

Adverse Event and Serious Adverse Event log

Event no.	Site	Subject no.	Event type (please see final page for definitions)	Related to IMP? (Y/N)	Expected reaction to IMP? (Y/N)	AE/SAE/ SUSAR?	Date of onset	Body system	Event description	Outcome (please see final page for outcome options)	Resolved? (Y/N)
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											

AE & SAE log v1, 5th Dec 2014

Event types

An Adverse Event (AE) is defined (according to CPMP/ICH/377/95) as "*Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment*". Any adverse event which affects a participant from the time they give informed consent to 30 days after the last study related contact (as defined in the protocol) should be recorded.

An adverse event is defined as serious if it:

1) Results in death
2) Is life threatening
3) Requires inpatient hospitalisation or prolongation of existing hospitalisation
4) Results in persistent or significant disability/incapacity, or
5) Is a congenital anomaly/birth defect

Please indicate one of these 5 types in the "Event type" column for all SAEs and SUSARs.

An SAE is defined as a SUSAR if it may be related to, and is an unexpected reaction to, the study intervention.

Outcomes

For the "Outcome" column, please indicate one of the following outcomes of the event:

1) Resolved
2) Resolved with sequelae
3) Improved
4) Persisting
5) Worsened
6) Fatal
7) Unknown

Appendix 7. Missing or incomplete questionnaire data

Reproduced from Snidvongs *et al.* Facet-joint injections for non-specific low back pain: a feasibility RCT (2017)[99]

Eleven participants did not complete, or incorrectly completed certain components of each questionnaire; this is detailed in table 20 below.

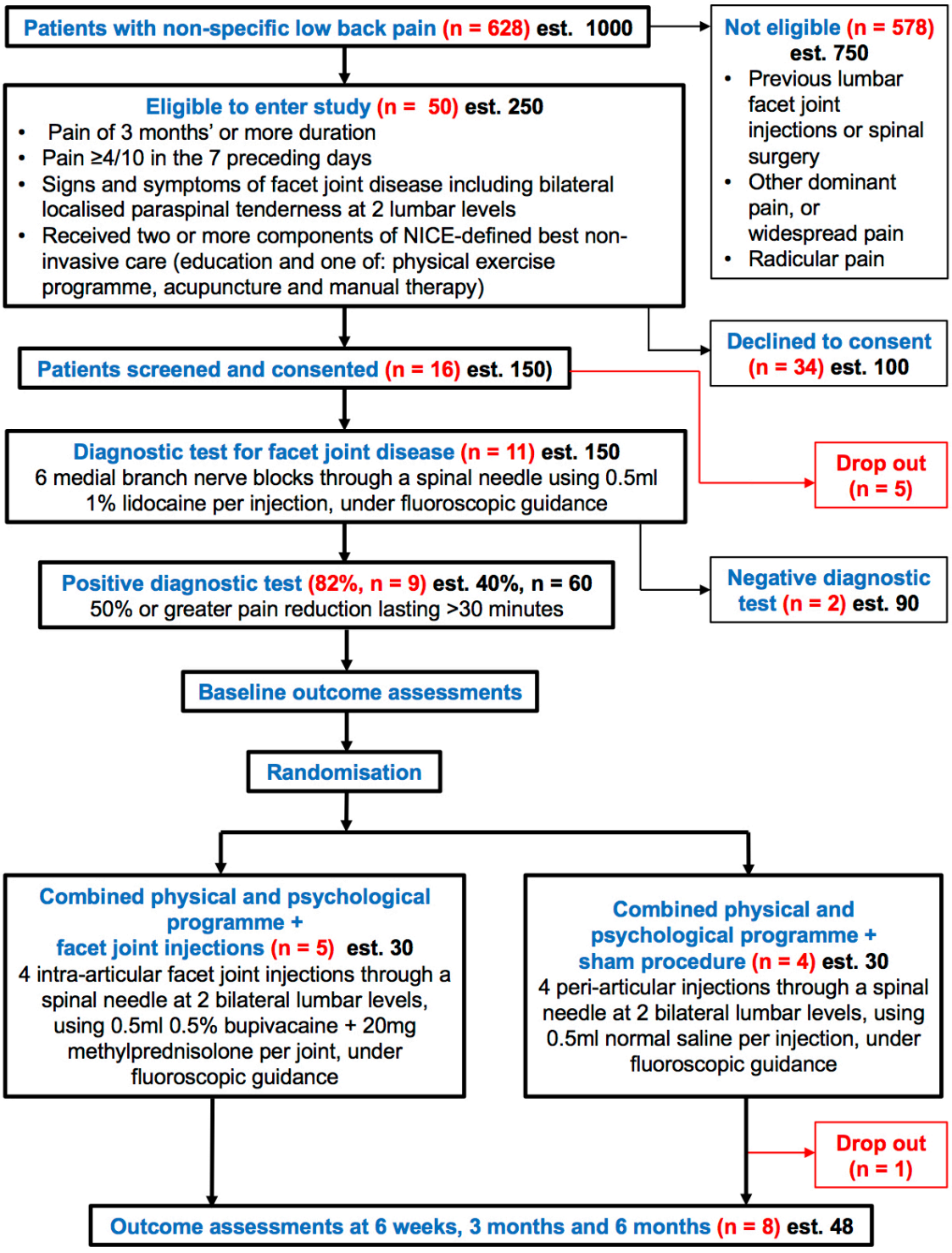
Table 20. Missing or incomplete questionnaire data

Participant number	Missing data				Details
	Baseline	6 weeks	3 months	6 months	
1002		All	All		
1003		BPI			'What treatments or medications are you receiving for your pain?' – missing
1004				BPI	'Please mark on the diagram the area of your pain' – spoiled
1005	SF-12				'Climbing several flights of stairs' – missing
1006			All		
1007	Oswestry				'Social life' – spoiled
1009		All			
1009	SF-12				'Physical health, limited to work, emotional problems, did work less carefully' – missing
1010	SF-MPQ-2				'Hot burning pain, splitting pain' – missing
	SF-12				'Did work less carefully' – missing
	Oswestry				'Personal care, sleeping' – spoiled; 'sex life' – missing
1011	SPS 6				'I felt hopeless about finishing certain work tasks, due to my health problems', 'At work, I was able to focus on achieving my goals despite my health problem' and 'Despite having my health problem, I felt energetic enough to complete all my work' – missing
1014	EQ-5D-5L				'Pain/discomfort' – missing
	Oswestry				'Sex life' – missing

Oswestry, Oswestry Low Back Pain Disability Questionnaire.

Appendix 8. CONSORT flow diagram showing the actual and estimated flow of participants through the study

Reproduced from Snidvongs et al.'s 'Facet-joint injections for non-specific low back pain: a feasibility RCT' (2017)[99]



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